CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209819Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	209819
Link to EDR	\\CDSESUB1\EVSPROD\NDA209819\0001
Submission Date	5/30/17; PDUFA date: 11/30/17
Submission Type	Priority Review; 505(b)(2)
Brand Name	SUBLOCADE
Generic Name	RBP-6000 (buprenorphine-ATRIGEL) depot; BUPRENORPHINE-ATRIGEL® ONE-MONTH DEPOT
Dosage Form and Strength	Solution for injection (100 and 300 mg buprenorphine)
Route of Administration	Subcutaneous injection
Proposed Indication	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.
Associated IND	107607
OCP Reviewer	David Lee, Ph.D. Michael Bewernitz, Ph.D.
OCP Team leader	Yun Xu, Ph.D. Kevin Krudys, Ph.D.

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1. EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application, NDA 209819, for SUBLOCADE, buprenorphine-ATRIGEL® one-month depot solution for injection; 100 and 300 mg buprenorphine, submitted on 5/30/17. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable. No further communication is necessary with the Applicant at this point. As of November 14, 2017, labeling negotiation is still ongoing with the Applicant.

The joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee (PDAC & DSaRM) meeting for NDA 209819, Sublocade subcutaneous Injection, submitted by Indivior Inc., was held on Tuesday, October 31st, 2017. The Committee discussed whether the data from the Phase 3 clinical trial and the results from the blockade study provided substantial evidence of effectiveness of RBP-6000 for the treatment of opioid use disorder (OUD) in patients who had undergone stabilization with a transmucosal buprenorphine product and whether there is a significant difference in the effectiveness between the two dose regimens tested, RBP-6000 300/300 mg and RBP-6000 300/100 mg. Additionally, the Committee discussed safety concerns (e.g., inadvertent intravenous injection) and Risk Evaluation and Mitigation Strategy (REMS) program. Finally, the Committee discussed whether the efficacy data are sufficient to outweigh the risks associated with this novel product and if both treatment regimens (RBP-6000 300/300 mg and RBP-6000 300/100 mg) should be approved. The Committee expressed opinions in favor of Sublocade, however, since there were many patients excluded initially from the study, the effectiveness in the 'real world' setting may be less than what was observed in the trial. There were discussions regarding dosing regimens as no clear efficacy differences were observed between 300/300 mg and 300/100 mg treatments. Considering the systemic exposure of the 300/300 mg dosing regimen is higher than the highest approved dosing regimen of sublingual buprenorphine product, the Committee commented that it may be prudent to use the lower dosing regimen, 300/100 mg on all patients initially, and only use 300/300 mg for those who do not gain sufficient benefit from 300/100 mg. Overall, the Committee recommended approval for the treatment of OUD in patients who have undergone stabilization to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine containing product.

Review Issue	**Recommendations and Comments**
Pivotal or supportive evidence of effectiveness	One Phase 3 trial, a single multiple-center, double-blind, placebo-controlled, 24-week safety and efficacy study, RB-US-13-0001, and, one opioid-blockade study, RB-US-13-0002, were conducted in patients with moderate to severe OUD who have undergone stabilization to suppress opioid withdrawal

	signs and symptoms with a transmucosal buprenorphine-containing product. To demonstrate buprenorphine delivered from Sublocade was adequate to reduce use of illicit opioids, the Phase 3 trial 13-0001 evaluated the following: primary and secondary endpoints: primary – the cumulative distribution function of the percentage weeks of abstinence measured by weekly UDS (Urine Drug Screen) negative for opioids and self-reports negative for illicit opioid from week 5 through 24; secondary - treatment success, where a responder was defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 5 and Week 24; Self-reports of illicit opioid use were obtained from Timeline Follow back (TLFB) interviews. The findings from the efficacy study indicated that Sublocade 100 mg once monthly and 300 mg once monthly maintenance doses met both primary and secondary endpoints in patients with moderate to severe OUD who have undergone stabilization to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. In the opioid blockade study 13-0002 the Applicant assessed the effect of RBP-6000 on visual analog scale (VAS) drug-liking measurements acquired during 12 hydromorphone challenge sessions; one challenge conducted each week for 12 weeks. Each hydromorphone challenge consisted of 3 consecutive days where each day a subject receives a single IM injection of 0 mg, 6 mg, or 18 mg hydromorphone in a blinded randomized manner. Subjects were stabilized on SL Suboxone for 2 weeks, received 300 mg SC RBP-6000 injection at the beginning of Week 1 and Week 5, with weekly hydromorphone challenge sessions from Weeks 1 to 12. On the weeks of RBP-6000 SC injection, hydromorphone challenges started 4 days after SC injection. The 300 mg dose provided effective blockade of opioid effects using the hydromorphone challenge tests. OCP's PK/PD analyses also provide supportive evidence of opioid blockade. There is a trend of increasing response (reduced drug-liking) with increasing opioid exposure. Also, higher buprenorphine exposures are required to reduce the drug-liking following an 18 mg hydrophone challenge compared to the 6 mg hydromorphone challenge. Please refer to section 4.4.3 for details. The Applicant conducted analyses to assess the relationship of % mu-opioid receptor availability and buprenorphine plasma

	concentration using data from Greenwald Study 1 and Greenwald Study 2. The Applicant's analysis shows that μORO increases with increasing buprenorphine exposure. The Applicant also applied an E_{max} model to assess the relationship between μORO and buprenorphine exposure. The result is that the maximum μORO in the data from the two Greenwald studies is 91.40% occupancy with an E_{max} of 0.67 ng/mL. Applicant assessed the μORO in n=2 subjects in a PET-imaging sub-study within Study 12-0005. The relationship between μORO and buprenorphine exposure from the n=2 subjects in the PET sub-study of 12-0005 are consistent with the data from the two Greenwald studies and the μORO E_{max} model predictions. Please refer to section 4.4.1 for details.
General dosing instructions	Sublocade is for subcutaneous injection only and must not be administered intravenously or intramuscularly. The recommended dose following a stabilization on a transmucosal buprenorphine-containing product is 300 mg monthly for the first two months followed by maintenance dose of 100 mg monthly. Sublocade 300 mg maintenance dose is optional for patients in the absence of medication toxicity and who do not response to the 100 mg monthly maintenance dose. The clinical efficacy of starting treatment with Sublocade 100 mg has not been studied. A patient who misses a dose of Sublocade should receive the next dose as soon as possible, with the following dose given no less than 26 days later. Unavoidable occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No formal assessment of Sublocade in pediatric population was conducted to date; however, buprenorphine has an orphan drug designation for the indication of opioid dependence (Section 526(a)(2)(B) of the FFDCA (application #93-752)). Thus, Sublocade is exempt from the PREA requirements. No dedicated RBP-6000 pharmacokinetic studies were conducted in hepatically-impaired or renally-impaired patients. With respect to hepatic impairment, the effect on buprenorphine PK has been previously evaluated with Suboxone sublingual tablets (2 mg/0.5 mg buprenorphine/naloxone) in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria (see Suboxone Film Prescribing Information 2017). The labeling states that "While no clinically relevant changes were observed in subjects with mild hepatic impairment, buprenorphine plasma exposure was increased by 64% and 181% in subjects with moderate and severe hepatic

	impairment, respectively, compared to healthy subjects." Due to the lack of first-pass effect, the effect of hepatic impairment on pharmacokinetics of RBP-6000 is expected to be less than the effect on Suboxone sublingual film. However, due to lacking of dedicated hepatic impairment study with Sublocade, the magnitude of PK changes in subjects with moderate or severe impairment is unknown. With respect to renal impairment, (b) (4) [redacted] No dedicated RBP-6000 pharmacokinetic studies were conducted to evaluate drug interactions. Buprenorphine is mainly metabolized via CYP3A4; co-administration of other drugs which are inhibitors or inducers of CYP3A4 activity can affect the pharmacokinetics of RBP-6000. Due to the lack of first-pass effects for RBP-6000, the magnitude of drug interaction with a 3A4 inhibitor or inducer is expected to be less for RBP-6000 in comparison to SL buprenorphine products (See Section 3.3 for discussion). With SL administration, a portion of the dose is typically swallowed. The Applicant refers to the information in listed drug products labels. However, due to lack of dedicated drug interaction studies with Sublocade and 3A4 inhibitors or inducers, the magnitude of PK changes in subjects with 3A4 inhibitors or inducers is unknown.
Labeling	See Section 2.4 for Labeling recommendation.
Bridge between the to-be-marketed and clinical trial formulations	Based on discussion with Office of Pharmaceutical Quality (OPQ) group, the Applicant agreed to use the same formulation used in clinical trials as the to-be-marketed formulation. See OPQ review for details.
Other (specify)	Not applicable.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

Indivior Inc., has submitted a New Drug Application (NDA) for SUBLOCADE ("Sublocade"), buprenorphine (18% w/w)-ATRIGEL® one-month depot solution for injection administered subcutaneously (SC) in the abdominal region for the treatment of moderate to severe opioid use disorder (OUD) in patients who have undergone stabilization to suppress opioid withdrawal signs

and symptoms with a transmucosal buprenorphine containing product. The proposed doses are 100 and 300 mg buprenorphine. The recommended dose by the Applicant, following a stabilization on a transmucosal buprenorphine-containing product, is 300 mg monthly (every 28 days); the dose may be decreased to 100 mg based upon tolerability. Sublocade is considered a single entity combination product (drug/device), presented in a prefilled syringe containing buprenorphine in the ATRIGEL drug delivery system. The ATRIGEL Delivery System is a non-aqueous solution consisting of a biodegradable polymer, 50:50 poly(DL-lactide-co-glycolide) with a carboxylic acid end group (PLGH) and a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). Sublocade forms a depot when injected subcutaneously and releases buprenorphine for a minimum of 28 days as the polymer biodegrades.

Sublocade should be used as part of a complete treatment plan to include counselling and psychosocial support. There is no currently approved parenterally administered extended release buprenorphine product for the treatment of OUD and this product may offer advantages over existing buprenorphine products, e.g., sublingual (SL) films/tablets, by improving patient compliance, reducing diversion/abuse, and reducing unintentional pediatric exposure. Sublocade original program was to deliver a similar buprenorphine exposure observed in SL products currently marketed; however, the development program was modified (discussion with the Agency) specifically to provide buprenorphine concentrations which would occupy approximately 70% or more of mu-opioid receptors in the brain. In turn, buprenorphine from the Sublocade would provide "opioid-receptor blockade" of exogenously administered opioids. In this regard, the Phase 3 pivotal study assesses the efficacy of two different dosing regimens of Sublocade, 300 mg every 28 days for 6 injections and 300 mg every 28 days for 2 injections followed by 100 mg every 28 days for 4 injections.

The Applicant requested a priority review status and has been granted. It is noted that Fast Track designation was granted by the Agency on May 23, 2016, which met the following criteria: the drug is intended to treat a serious condition and address an unmet medical need. Additionally, the Applicant stated that buprenorphine has an orphan drug designation for the indication of opioid dependence. In support of this, the Applicant submitted the 2002 Suboxone tablet Orphan Status Approval letter dated June 15, 1994, which states that buprenorphine qualified for orphan designation for the treatment of opiate addiction in opiate users under Section 526(a)(2)(B) of the FFDCA (application #93-752). Thus, Sublocade is exempt from the PREA requirements.

The Applicant submitted the current NDA through the 505(b)(2) pathway. The Applicant indicated this application is relying for approval, in part, on the Agency's findings of safety and efficacy of Subutex SL tablet, N 20732. Additionally, it relies on published literature to support the safety assessment of the excipients which form the ATRIGEL delivery technology: safety assessment for N-methyl-2-pyrrolidone (NMP) and for 50:50 poly(lactide-co-glycolide). The Applicant stated that applicable information from the Subutex product label has been included in the Sublocade draft Package Insert. Four key meetings were held with the Agency regarding Sublocade drug development: a pre-IND meeting was held on 4/27/10; an End-of-Phase 2 meeting was held on 9/30/14; Type C guidance meeting was held on 9/28/16; and, a pre-NDA meeting was held on 12/14/16.

Sublocade program consisted of seven clinical studies, which were conducted under IND 107607 (Table 1). The objectives for the development of Sublocade were to: achieve opioid blockade starting from the first dose of treatment across the entire dosing interval at concentrations of buprenorphine that are safe and well tolerated, negating the need for rescue medications, achieve clinically significant control of craving and withdrawal symptoms, prevent illicit opioid use, and limit the possibility of misuse and diversion, and enable treatment concordance. The clinical trials conducted to support the development program included: one Phase 3 double blind placebo controlled study for efficacy and safety (RB-US-13-0001), one Phase 3 Open label study for long-term safety (RB-US-13-0003), and, one opioid blockade study (RB-US-13-0002).

Sublocade has been developed with the following designations, which the designation will be used interchangeably in this review: RBP-6000 (buprenorphine-ATRIGEL) depot; Buprenorphine-ATRIGEL® One-Month Depot. The final to-be-marketed formulation was used in all clinical trials and in the manufacture of the registration batches.

Table 1 Listings of Sublocade clinical studies

Study Number/ Phase/ Status	Study Design	Planned Sample Size	RBP-6000 Dose (N) Induction/Dose-stabilization Medication (Safety Population)	Population	Objective(s)
RB-US-10-0011/ Phase 1/ Completed	SS, FTIH, SD, PK, OL	18 enrolled to obtain at least 6 completers	Single RBP-6000 SC dose 20 mg (N=12)[No buprenorphine induction/dose stabilization period]	Opioid-dependent (DSM-IV-TR) methadone treatment-seeking subjects (males and females) ≥ 18 to ≤ 60 years of age BMI ≥ 18.0 to ≤ 33.0 kg/m2	Safety; tolerability; PK profile; Determine dose
RB-US-11-0020/ Phase 1/ Completed	MC, SAD, PK, OL	12 enrolled per cohort to obtain 18 completers (at least 6 completers per cohort)	Three cohorts:50 (N=12), 100 (N=12), or 200 (N=12) mg [No buprenorphine induction/dose-stabilization for Cohorts 1-3] Cohort 4 (N=15): 100 mg after induction/dose stabilization of SUBOXONE SL tablets; 12 mg/day for 5 days followed by RBP-6000 containing 100 mg buprenorphine	Opioid-dependent (DSM-IV-TR) treatment-seeking subjects (males and females) ≥ 18 to ≤ 65 years of age BMI ≥ 18.0 to ≤ 33.0 kg/m2	Safety; tolerability; PK profile; Explore PD markers
RB-US-13-0006/ Phase 1/ Completed	SS, R, SD, PK, OL Using PLGH Polymer of 2 Different MW (Low and High MWs as Test) in Comparison to Intermediate MW (Ref)	Approximately 48 enrolled to obtain at least 36 completers	Single SC dose 300 mg (N=47) [Using SUBOXONE SL film, induction/dose stabilization phase, 2 to 8 mg/day for 1 day; 2 to 12 mg/day for 1-2 days; and 12 mg for 5 days]	Opioid-dependent (DSM-5) treatment-seeking subjects (males and females) ≥ 18 to ≤ 65 years of age BMI ≥ 18.0 to ≤ 35.0 kg/m2	Safety; tolerability; PK profile

RB-US-12-0005/ Phase 2A/ Completed	MC, MD, PK, PD, OL (PET sub-study, 2 subjects)	15 enrolled per cohort to obtain at least 36 completers (at least 6 completers per cohort)	50 (N=15), 100 (N=30), 200 (N=30), or 300 (N=14) mg in repeated (4 or 6) SC injections separated by 28 days (Two of the 89 subjects participated in a PET Scan sub-study) [Induction/ dose stabilization period with SUBUTEX SL tablets, 13 day, 8 to 24 mg]	Opioid-dependent (DSM-IV-TR) treatment-seeking subjects inducted and then stabilized on SUBUTEX dose of 8, 12, 14, 24 mg or 8-24 mg (13-day lead-in phase). males and females ≥ 18 to ≤ 65 years of age BMI ≥ 18.0 to ≤ 33.0 kg/m2	Safety; tolerability; PK/PD profile
RB-US-13-0002/ Phase 2/ Completed	SS, **OB**, MD, PK	At least 24 completers	300 mg in each of 2 SC injections separated by 28 days (N=39) [Hydromorphone challenge; Subjects who had an acceptable response to hydromorphone challenge were inducted and stabilized (over a 13- to 14-day period) on SUBOXONE SL film to reach a final dosage of 8-24 mg/day] Hydromorphone challenges were conducted pre-treatment (baseline at Days -17, -16 and -15), during induction/dose stabilization (Days -3, -2 and -1), and 12 weeks with HM 6 or 18 mg, or placebo.	Opioid-dependent (DSM-5), not treatment-seeking subjects (males and females) ≥ 18 to ≤ 55 years of age BMI ≥ 18.0 to ≤ 33.0 kg/m2	Blockade of subjective opioid effects; PK profile, safety
RB-US-13-0001/ Phase 3/ Completed	MC, MD, R, DB, PC, 24-week efficacy, safety and tolerability (**Ph3DB**)	Approximately 470 (188 enrolled in 300 300 active group, 188 enrolled in 300 100 active group and 94 in Placebo group)	300/300 active group: 300 mg for 6 injections separated by 28 days 300/100 active group: 300 mg for first 2 injections followed by 100 mg for subsequent 4 injections separated by 28 days Placebo group: Volume-matched (47 to 300/300 group; 47 to 300/100 group) (N = 504) [Induction/dose stabilization period SUBOXONE SL film day induction 2-24 mg, then to 11-day dose stabilization 8-24 mg (no taper, n=342; taper, n=162)]	Opioid-dependent (DSM-5) treatment-seeking subjects inducted onto SUBOXONE SL film for 3 days (males and females) ≥ 18 to ≤ 65 years of age BMI ≥ 18.0 to ≤ 35.0 kg/m2	Efficacy & safety; population PK
RB-US-13-0003/ Phase 3/ Ongoing (interim CSR (safety only) provided; final analysis underway)	MC, MD, OL long-term safety and tolerability (extension of RB-US-13-0001) (**Ph3OL**)	Approximately 600 to provide additional safety data on at least 500 subjects exposed to RBP-6000 for at least 6 months and at least 100 subjects exposed to RBP-6000 for at least 12 months	All subjects received an initial 300 mg injection. This was followed by: De novo subjects: 300 mg or 100 mg in each of 12 SC injections separated by 28 days Rollovers: 300 mg or 100 mg in each of 6 SC injections separated by 28 days [N = 672 (415 de novo, 257 rollover)] [Induction/dose stabilization period with SUBOXONE SL film: 3-day induction 2/4-8/24 mg/day, then 1- to 11-day dose stabilization 8-24 mg/day]	Opioid-dependent (DSM-5) treatment-seeking subjects (males and females) ≥ 18 to ≤ 65 years of age BMI ≥ 18.0 to ≤ 35.0 kg/m2	Long-term; Efficacy & safety; population PK

The current review focused on Studies RB-US-11-0020 (SAD; with and without buprenorphine sublingual stabilization steps), RB-US-12-0005 (MD; with buprenorphine sublingual stabilization steps) for the proposed 100 and 300 mg doses specified and to support in the Label. Additionally, Studies RB-US-13-0006 (SD; with buprenorphine sublingual stabilization steps) and RB-US-13-0002 (2 doses of Sublocade; with buprenorphine sublingual stabilization steps) were assessed for buprenorphine release profile from Sublocade. Study RB-US-10-0011 was not reviewed due to this study assessing 20 mg Sublocade. Population PK analyses information from 2 Phase 3 trials, RB-US-13-0001 and RB-US-13-0003, were assessed to address the drug interaction potentials (e.g., 3A4 inducer/inhibitor on buprenorphine exposure), special populations (e.g., renal impairment, age, race, sex, etc.), and, various clinical factors, e.g., buprenorphine exposure due to the body mass index, re-injection within same abdominal quadrant, buprenorphine exposure due to missed doses up to 2 weeks and treatment interruption, etc. Additionally, population PK/PD analyses were assessed regarding the relationship between buprenorphine concentrations and response observed, such as, for illicit opioid use (e.g., subjects using opioids by the injectable route at baseline), opioid craving, and withdrawal symptoms (Clinical Opiate Withdrawal Scale/Subjective Opiate Withdrawal Scale), and, the relationship between buprenorphine plasma concentration and μ-opioid receptor occupancy (μORO) in the brain, as appropriate.

Study RB-US-13-0001 was a Phase 3, randomized, double-blind, placebo-controlled, multi-center study which assessed the efficacy, safety and tolerability of multiple Sublocade injections over 24 weeks [Treatment 1: Sublocade 300 mg for 6 injections (once every 28 days); Treatment 2: Sublocade 300 mg for 2 injections (followed by 100 mg for 4 injections (once every 28 days)] in treatment-seeking subjects with a diagnosis of moderate or severe OUD. Subjects were inducted onto Suboxone SL film for 3 days, followed by a Suboxone SL film run-in dose-adjustment period (4- to 11-day) to achieve buprenorphine doses ranging from 8 to 24 mg/day. For placebo treatments, patients were administered a placebo injection that was volume-matched for Sublocade 300 mg or 100 mg injections. The primary efficacy was assessed by centrally tested urine drug screen (UDS) results (urine samples negative for opioids) and self-reported illicit opioid (percentage abstinence) use as recorded by the patient from Week 5 through Week 24. Additionally, scores for Opioid Craving VAS, Clinical Global Impression-Severity (CGI-S) scale, Clinical Global Impression-Improvement (CGI-I) scale, COWS and SOWS were assessed. Urine drug screens and self-reports were assessed at screening, and on a weekly basis following each Sublocade SC injections or placebo (Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, 106, 113, 120, 127, 134, 141, 148, 155, 162 and 169), as well as at a safety follow-up visit (Day 197). Urine drug screens were also assessed on the day after each SC injection at 24 h post-dose (Days 2, 30, 58, 86, 114 and 142). The reader is referred to Clinical Review by Drs. Emily Deng and Feng Li, Office of New Drug (OND) and Office of Biostatistics (OB), respectively.

Study RB-US-13-0002 was a double-blind, placebo-controlled, two of Sublocade 300 mg injections (28-day apart; Day 1 and Day 29) study in non-treatment-seeking subjects with moderate to severe OUD to assess the blockade of hydromorphone's subjective effects. This study is considered as supportive evidence for efficacy since only one well controlled Phase 3 study was conducted. Patients were treated with up to 24 mg Suboxone in the lead-in phase. Buprenorphine blood samples were collected at: Day 1 – pre-dose, Days 2, 5-7, 12-14, 19-21, 26-28, Day 29 – pre-dose, Days 30, 33-35, 40-42, 47-49, 54-56, 61-63, 68-70, 75-77, and 82-84. The primary objective was to assess "Drug Liking" scores measured after challenge with 6mg or 18mg of

intramuscular (IM) hydromorphone with placebo. The reader is referred to Control Substance Staff (CSS) Review by Drs. Alan Trachtenberg and Wei Liu, CSS and OB, respectively.

Clinical pharmacology findings

Single dose

Study RB-US-11-0020 evaluated pharmacokinetics of a single dose of 50 mg, 100 mg, 200 mg RBP-6000 SC injection, and, for a single dose of 100 mg RBP-6000 SC injection following a 7-day buprenorphine sublingual stabilization or "lead-in" phase to achieve a stable buprenorphine dose of 12 mg/day in subjects with opioid use disorder. After a single dose RBP-6000 100 mg SC injection (without buprenorphine sublingual stabilization or "lead-in" phase prior to SC injection), the buprenorphine peak was observed approximately 24 h post administration. Observed buprenorphine levels declined to a plateau until the end of the dosing interval indicating that buprenorphine is consistently released from the RBP-6000 during the dosing interval. Buprenorphine pharmacokinetic parameters are presented in Table 2.

Table 2 Buprenorphine pharmacokinetic parameters from a single dose RBP-6000 50, 100 and 200 mg in Study RB-US-11-0020 (note: Cohort 2: 100 mg)

Parameter	Statistic	RBP-6000 alone			RBP-6000 + Suboxone SL
		Cohort 1 50 mg	Cohort 2 100 mg	Cohort 3 200 mg	Cohort 4 100 mg
Cavg (ng/mL)	n	12	12	12	10
	Mean	0.370	0.633	1.138	0.951
	%CV	27.4	16.6	25.7	32.5
Cmax (ng/mL)	n	12	12	12	12
	Mean	1.051	1.537	2.427	2.285
	%CV	35.6	16.4	20.9	23.2
Cmin (ng/mL)	n	12	12	12	12
	Mean	0.059	0.089	0.148	0.275
	%CV	56.1	44.3	67.8	64.3
Tmax (hr)	n	12	12	12	12
	Median	24.0	24.0	24.0	18.0
	Min, Max	4.00, 24.03	24.0, 48.0	4.00, 144.0	4.00, 24.0

%CV = coefficient of variation; hr = hour; Max = maximum; Min = minimum; PK = pharmacokinetic; QD = once daily; SC = subcutaneous; SD = standard deviation; SL = sublingual
Cohort 1 = a single SC injection of RBP-6000 containing 50 mg buprenorphine.
Cohort 2 = a single SC injection of RBP-6000 containing 100 mg buprenorphine.
Cohort 3 = a single SC injection of RBP-6000 containing 200 mg buprenorphine.
Cohort 4 = QD dosing with SUBOXONE SL, 8 mg (two 4 mg doses approximately 3 hours apart) on Day -7 and 12 mg on Days -6 through -1.
Source: Table 14.2.1.3, Listing 16.2.6.2.1, Listing 16.2.6.2.2, and Listing 16.2.6.2.3

Discussion on the molecular weight of PLGH polymer in Sublocade formulation

During Sublocade formulation development, the effects of the MW of PLGH and NMP content (b) (4) were investigated in vitro (b) (4)

Additionally, the Applicant proposed Sublocade molecular weight (MW) Acceptance Criteria of (b) (4) kilodaltons (kDa). A comparative bioavailability study (Study RB-US-13-0006) was conducted to assess the buprenorphine exposure of Sublocade formulated with different MW of PLGH, namely, from 9 kDa to 17 kDa MW of PLGH. The MW range evaluated in Study RB-US-13-0006 covered the formulations used in other clinical studies, including the pivotal Phase 3 trial, RB-US-13-0001 ((b) (4) kDa; Phase 3 Safety Extension trial, RB-US-13-0003, utilized (b) (4) kDa). Study RB-US-11-0006 was a single-center, randomized, open-label, single-dose, parallel-group study in subjects with OUD who have undergone buprenorphine sublingual stabilization (final stabilized Suboxone film dose of 12 mg) or "lead-in" phase. This study evaluated pharmacokinetics of single dose of RBP-6000 300 mg formulated with three different PLGH MW polymers: 9 kDa of PLGH polymer (RBP-6000 PLGH A; test arm), 14 kDa of PLGH polymer (RBP-6000 PLGH C; reference arm), and, 17 kDa of PLGH polymer (RBP-6000 PLGH B, test arm). Buprenorphine pharmacokinetic parameters are presented Table 3.

Table 3 Single-dose RBP-6000 300 mg pharmacokinetic parameters in Study RB-US-13-0006

Parameter		RBP-6000 PLGH A (9 kDa)	RBP-6000 PLGH B (17 kDa)	RBP-6000 PLGH C (14 kDa)
Cmax (ng/mL)	n	16	15	16
	Mean	7.40	5.07	5.93
	SD	2.550	1.734	1.603
AUC0-28days (h*ng/mL)	n	13	13	13
	Mean	1550	1040	1230
	SD	512.7	310.0	422.9
AUClast (h*ng/mL)	n	16	15	16
	Mean	2140	1730	1830
	SD	1140	864.9	941.5
Tmax (h)	n	16	15	16
	Minimum	4.00	12.0	4.00
	Median	16.0	20.0	20.0
	Maximum	24.0	28.0	24.0
Hour 312 (Day 14) (ng/mL)	n	13	13	13
	Mean	2.21	1.23	1.64
	SD	0.73	0.45	0.75
Hour 504 (Day 22) (ng/mL)	n	13	13	13
	Mean	1.97	1.21	1.61
	SD	0.66	0.48	0.56
Hour 672 (Day 29) (ng/mL)	n	13	13	13
	Mean	1.83	1.30	1.43
	SD	0.68	0.62	0.47

RBP-6000 PLGH A: RBP-6000 300 mg buprenorphine formulated with 9 kDa PLGH polymer (test treatment), subcutaneous (SC) injection
RBP-6000 PLGH B: RBP-6000 300 mg buprenorphine formulated with 17 kDa PLGH polymer (test treatment), SC injection
RBP-6000 PLGH C RBP-6000 300 mg buprenorphine formulated with 14 kDa PLGH polymer (reference treatment), SC injection
Hour 312, 504, 672: Table 14.2.2 Summary of plasma concentration of buprenorphine (RBP-6000 phase) Pharmacokinetic set
Source: rbus130006-body.pdf; End-of-Text Table 14.2.6.

The results indicated that 9 and 17 kDa formulations are not bioequivalent to 14 kDa formulation. During a team discussion, the Office of Pharmaceutical Quality, Office of New Drug Products (OPQ, ONDP) team indicated that Acceptance Criteria of (b) (4) kDa will most likely not be agreed with the Applicant and suggested a new Acceptance Criteria of (b) (4) kDa for the entire

expiry period [redacted] selected to ensure the end of expiry) with 'newly produced' commercial batches in the ranges of [redacted] kDa. The review team decided that there should be no issues with [redacted] limit of [redacted] kDa, as [redacted] kDa PLGH MW formulation was assessed in Phase 3 trials. Similarly, the clinical team commented that it is not likely to have safety related concerns with the higher buprenorphine exposure with [redacted] limit of [redacted]kDa, since most of the buprenorphine levels were overlapping between [redacted] kDa ([redacted]MW) formulations, and there is no clear evidence that the higher buprenorphine exposure observed with [redacted]kDa are associated with signals of adverse events.

Multiple dose

Study RB-US-12-0005 was an open-label, multicenter study which evaluated pharmacokinetics of multiple dose Sublocade injections in adult subjects seeking treatment for opioid dependence previously on buprenorphine SL treatment. Subjects were stabilized over a 13-day period on various doses of Subutex SL tablets followed by 50, 100, 200 mg or 300 mg Sublocade multiple dose injections (Table 4).

Table 4 Sublocade treatment doses cohorts Subutex SL lead-in phase

	Cohort									
	1	2	3	4	5	6				
Subutex SL (mg)	8	12	24	8	14	8	12	16	20	24
Sublocade (mg)	50	100	200	100	200	300				
	4 Sublocade injections at 28-day intervals					Up to 6 Sublocade injections at 28-day intervals				

Summary of PK parameters for the overall phase for buprenorphine is provided in Table 5.

Table 5 Buprenorphine Plasma Pharmacokinetic Parameters Summary – Overall Phase (Population: PK) separated by injection days, Day 1 (Injection 1), Day 85 (Injection 4) and Day 141 (Injection 6)

			SUBUTEX SL; RBP-6000					
Parameter	**Time point**	**Statistic**	**Cohort 1 8 mg; 50 mg**	**Cohort 2 12 mg; 100 mg**	**Cohort 3 24 mg; 200 mg**	**Cohort 4 8 mg; 100 mg**	**Cohort 5 14 mg; 200 mg**	**Cohort 6 Total; 300 mg**
AUC 0-24 (OVR) (hr*ng/mL)	DAY 1 DOSE	n	15	15	14	15	12	14
		Mean	24.922	36.981	55.291	31.747	50.034	85.090
		SD	6.4450	14.3565	17.0179	13.2180	11.4899	28.7163
		%CV	25.9	38.8	30.8	41.6	23.0	33.7
		Median	24.278	36.699	52.430	30.173	47.181	86.170
		Min,Max	13.02, 35.31	13.96, 65.84	32.63, 93.06	15.89, 65.49	35.11, 72.78	30.17, 128.93
		Geometric Mean	24.091	34.334	53.082	29.496	48.901	79.886

AUCtau (hr*ng/mL)	DAY 1 DOSE	n	15	14	13	14	14	11
		Mean	246.650	461.366	642.010	413.438	756.053	1268.012
		SD	54.9881	142.2166	228.0284	133.0365	223.8099	389.6719
		%CV	22.3	30.8	35.5	32.2	29.6	30.7
		Median	256.246	451.168	602.314	388.270	694.699	1131.870
		Min,Max	148.95, 363.20	273.04, 723.10	381.93, 1226.09	210.95, 655.34	426.71, 1150.73	889.92, 1995.21
		Geometric Mean	240.620	442.112	610.630	394.190	726.666	1218.902
Cavg (ng/mL)	DAY 1 DOSE	n	15	14	13	14	14	11
		Mean	0.367	0.687	0.955	0.615	1.125	1.887
		SD	0.0818	0.2116	0.3393	0.1980	0.3331	0.5799
		%CV	22.3	30.8	35.5	32.2	29.6	30.7
		Median	0.381	0.671	0.896	0.578	1.034	1.684
		Min,Max	0.22, 0.54	0.41, 1.08	0.57, 1.82	0.31, 0.98	0.63, 1.71	1.32, 2.97
		Geometric Mean	0.358	0.658	0.909	0.587	1.081	1.814
Cmax (OVR) (ng/mL)	DAY 1 DOSE	n	15	15	14	15	15	14
		Mean	1.352	2.023	2.732	1.686	2.861	4.817
		SD	0.4641	0.8251	0.7866	0.6200	0.7136	1.4337
		%CV	34.3	40.8	28.8	36.8	24.9	29.8
		Median	1.280	1.850	2.570	1.530	2.670	4.750
		Min,Max	0.66, 2.61	0.94, 3.74	1.71, 4.61	0.87, 3.14	1.80, 4.11	2.41, 6.74
		Geometric Mean	1.287	1.870	2.638	1.588	2.781	4.604
Cmin (OVR) (ng/mL)	DAY 1 DOSE	n	15	15	14	15	15	14
		Mean	0.206	0.375	0.589	0.410	0.700	0.836
		SD	0.0556	0.1001	0.2522	0.1955	0.2196	0.3756
		%CV	27.0	26.7	42.8	47.6	31.4	44.9
		Median	0.207	0.381	0.497	0.344	0.626	0.860
		Min,Max	0.09, 0.30	0.23, 0.65	0.30, 1.29	0.17, 0.87	0.40, 1.12	0.40, 1.71
		Geometric Mean	0.198	0.364	0.548	0.375	0.670	0.762
Tmax (OVR) (hr)	DAY 1 DOSE	n	15	15	14	15	15	14
		Mean	15.470	47.078	18.720	24.933	21.072	17.429
		SD	6.2117	102.4253	7.6313	13.1555	10.7949	11.0225
		%CV	40.2	217.6	40.8	52.8	51.2	63.2
		Median	20.000	20.000	20.000	20.000	20.000	20.000
		Min,Max	4.00, 20.05	4.00, 414.17	6.00, 30.00	4.00, 48.00	6.00, 48.00	4.00, 32.00
		Geometric Mean	13.709	20.533	16.981	21.513	18.198	13.500
AUC 0-24 (OVR) (hr*ng/mL)	DAY 85 DOSE	n	11	12	11	10	8	7
		Mean	35.250	56.231	91.197	47.633	81.417	178.109
		SD	14.5405	15.6411	27.4005	9.6147	18.3829	43.2176
		%CV	41.2	27.8	30.0	20.2	22.6	24.3
		Median	30.331	54.655	82.736	46.181	77.622	171.460
		Min,Max	22.07, 70.47	27.77, 83.29	60.57, 140.20	34.38, 62.71	61.15, 112.41	122.16, 255.64
		Geometric Mean	33.131	54.058	87.698	46.767	79.666	173.784
AUCtau (hr*ng/mL)	DAY 85 DOSE	n	10	11	9	8	7	2
		Mean	667.611	1272.047	1932.068	1275.098	2051.989	3230.873
		SD	254.2712	434.1013	455.1540	252.8500	466.6935	430.6718
		%CV	38.1	34.1	23.6	19.8	22.7	13.3
		Median	652.871	1252.517	1713.514	1341.354	1929.187	3230.873
		Min,Max	318.33, 1070.70	854.45, 2406.25	1445.06, 2713.9	770.77, 1583.65	1665.06, 3025.55	2926.34, 3535.40
		Geometric Mean	622.695	1217.720	1887.775	1249.045	2013.339	3216.489

Cavg (ng/mL)	DAY 85 DOSE	n	10	11	9	8	7	2
		Mean	0.993	1.893	2.875	1.897	3.054	4.808
		SD	0.3784	0.6460	0.6773	0.3763	0.6945	0.6409
		%CV	38.1	34.1	23.6	19.8	22.7	13.3
		Median	0.972	1.864	2.550	1.996	2.871	4.808
		Min,Max	0.47, 1.59	1.27, 3.58	2.15, 4.04	1.15, 2.36	2.48, 4.50	4.35, 5.26
		Geometric Mean	0.927	1.812	2.809	1.859	2.996	4.786
Cmax (OVR) (ng/mL)	DAY 85 DOSE	n	11	12	11	10	11	7
		Mean	2.085	3.066	4.526	2.554	4.404	9.637
		SD	1.4381	0.8658	1.3078	0.4775	0.9231	2.3409
		%CV	69.0	28.2	28.9	18.7	21.0	24.3
		Median	1.650	2.935	4.230	2.405	4.040	9.840
		Min,Max	1.10, 6.26	2.01, 5.07	2.88, 6.64	2.10, 3.43	3.02, 6.16	6.46, 12.60
		Geometric Mean	1.835	2.964	4.360	2.517	4.317	9.383
Cmin (OVR) (ng/mL)	DAY 85 DOSE	n	11	12	11	10	11	7
		Mean	0.557	1.263	2.121	1.180	2.256	4.043
		SD	0.1559	0.3574	0.4689	0.2803	0.6472	0.6936
		%CV	28.0	28.3	22.1	23.8	28.7	17.2
		Median	0.606	1.220	2.240	1.205	2.370	3.820
		Min,Max	0.29, 0.78	0.75, 1.94	1.38, 2.74	0.83, 1.74	1.24, 3.13	3.04, 5.19
		Geometric Mean	0.535	1.216	2.071	1.151	2.166	3.992
Tmax (OVR) (hr)	DAY 85 DOSE	n	11	12	11	10	11	7
		Mean	18.727	60.082	23.470	75.387	26.182	21.429
		SD	5.6761	94.6239	7.1642	160.2744	15.4261	11.8161
		%CV	30.3	157.5	30.5	212.6	58.9	55.1
		Median	20.000	20.000	20.083	24.000	24.000	24.000
		Min,Max	2.00, 24.00	12.00, 315.95	8.00, 30.08	4.00, 529.83	4.00, 48.00	4.00, 36.00
		Geometric Mean	16.494	31.181	22.140	28.254	21.213	17.280
AUC 0-24 (OVR) (hr*ng/mL)	DAY 141 DOSE	n						1
		Mean						155.779
		SD						.
		%CV						.
		Median						155.779
		Min,Max						155.78, 155.78
		Geometric Mean						155.779
AUCtau (hr*ng/mL)	DAY 141 DOSE	n					2	
		Mean					2585.976	
		SD					276.6695	
		%CV					10.7	
		Median					2585.976	
		Min,Max					2390.34, 2781.61	
		Geometric Mean					2578.566	
Cavg (ng/mL)	DAY 141 DOSE	n					2	
		Mean					3.848	
		SD					0.4117	
		%CV					10.7	
		Median					3.848	
		Min,Max					3.56, 4.14	
		Geometric Mean					3.837	

Cmax (OVR) (ng/mL)	DAY 141 DOSE	n					2	1
		Mean					5.015	7.140
		SD					0.8980	
		%CV					17.9	
		Median					5.015	7.140
		Min,Max					4.38, 5.65	7.14, 7.14
		Geometric Mean					4.975	7.140
Cmin (OVR) (ng/mL)	DAY 141 DOSE	n					2	1
		Mean					2.910	4.290
		SD					0.7354	
		%CV					25.3	
		Median					2.910	4.290
		Min,Max					2.39, 3.43	4.29, 4.29
		Geometric Mean					2.863	4.290
Tmax (OVR) (hr)	DAY 141 DOSE	n					2	1
		Mean					24.000	24.350
		SD					0.0000	
		%CV					0.0	
		Median					24.000	24.350
		Min,Max					24.00, 24.00	24.35, 24.35
		Geometric Mean					24.000	24.350

Subjects were dosed with SUBUTEX SL tablet followed by SC injections of RBP-6000 containing buprenorphine.
The Cohort 6 column is the total for the 8 mg, 12 mg, 16 mg, 20 mg, and 24 mg SUBUTEX columns from Table 14.2.1.3.
Source: Table 14.2.1.3

After Sublocade injection, an initial buprenorphine peak was observed and the median Tmax occurred at 24 hours after injection. After the initial buprenorphine peak, the plasma buprenorphine concentrations decreased slowly and stable plasma buprenorphine concentrations were reached by approximately Week 2.

Study RB-US-13-0002 was a double-blind, placebo-controlled, *two* Sublocade 300 mg injections (28-day apart; Day 1 and Day 29) study in non-treatment-seeking subjects with moderate to severe OUD to assess the blockade of hydromorphone's subjective effects. Patients were treated with up to 24 mg Suboxone in the lead-in phase. Buprenorphine blood samples were collected at: Day 1 – pre-dose, Days 2, 5-7, 12-14, 19-21, 26-28, Day 29 – pre-dose, Days 30, 33-35, 40-42, 47-49, 54-56, 61-63, 68-70, 75-77, and 82-84. The primary objective was to assess "Drug Liking" scores measured after challenge with 6mg or 18mg of intramuscular (IM) hydromorphone with placebo. Following SC RBP-6000 administration, mean buprenorphine plasma concentrations were slightly higher following the second dose on Day 29 when compared with the first dose on Day 1. For individual buprenorphine concentrations observed in Days 5-7, 12-14, 19-21, 26-28 are presented in Table 6.

Table 6 Observed buprenorphine concentrations (ng/mL) on Days 5-7, 12-14, 19-21, 26-28

Parameter	Day 05	Day 06	Day 07	Day 12	Day 13	Day 14	Day 19	Day 20	Day 21	Day 26	Day 27	Day 28
N	38	37	37	36	35	34	33	33	33	30	30	29
Mean	2.30	1.97	1.96	1.88	1.89	1.94	1.93	1.88	1.91	1.77	1.75	1.79
SD	0.81	0.72	0.79	0.74	0.65	0.63	0.68	0.64	0.60	0.58	0.62	0.68
Min	0.10	0.78	0.74	0.71	0.69	0.83	0.74	0.73	0.86	1.07	0.98	1.03

Max	4.65	3.70	4.03	4.70	3.51	3.58	4.34	3.87	3.59	3.82	3.86	3.89

The observed buprenorphine concentrations on Days 5 to 28 after the 1st injection ranged from 1.75 to 2.3 ng/mL. The buprenorphine concentrations after 2nd injection appear to be above 2 ng/mL from Days 29 to 84.

Steady-state assessment

Following multiple SC injections of RBP-6000, the statistical analysis indicated that the steady-state levels of buprenorphine were achieved by the by the fourth injection (Day 85) in the 300-mg dose group. The steady-state was not achieved for the 100-mg dose group based on the data for four SC injections. However, according to PK simulations, the 100-mg dose group appear to reach steady state by the sixth injections; similar findings were observed for the 300-mg dose group.

Time-to-approach or drop below limit of quantification after Sublocade final dose

The buprenorphine concentration-time profiles following a single dose (Study RB-US-11-0020) of Sublocade indicated that buprenorphine levels were observed on Day 150 timepoint (at approximately 0.3 ng/mL). It is noted that the lower limit of quantitation (LLOQ) for buprenorphine is found to be at 0.025 to 0.05 ng/mL.

The time duration for which the drug remained in the plasma after the final dose of Sublocade is necessary to inform a label statement regarding discontinuation of Sublocade. The review team was interested to know how long after discontinuing RBP-6000 can patients be expected to test positive on a buprenorphine drug test. As such, the clinical pharmacology team was asked to investigate the buprenorphine profile after the last injection of Sublocade at steady-state. Simulations were conducted to generate a profile following the final dose of Sublocade at steady-state for each proposed maintenance dose level (100 mg once monthly and 300 mg once monthly). Overall, for both maintenance dose levels of 100 and 300 mg once monthly, buprenorphine plasma concentration remains above the LLOQ for up to 12 months.

Effect of increasing Sublocade dosing interval on buprenorphine levels

Based on the relatively flat buprenorphine profile observed after administration of Sublocade and due to concerns about safety at the 300-mg dose, the possibility of a longer dosing interval on Sublocade exposure was assessed based on simulations (using the Applicant's model-after the final dose of Sublocade at steady-state (b) (4)).

Overall, the simulations suggest that exposures for a maintenance dose of 300 mg once every other month are likely to be within the exposures achieved with maintenance doses of 100 mg once monthly and 300 mg once monthly. As both the 100 and 300 mg once monthly maintenance dose levels demonstrated efficacy in the pivotal trial, this finding suggests that 300 mg once every other month may be an efficacious dose regimen, which could reduce the number of injections by 50% (6 instead of 12 injections per year). Based on discussions with Clinical team, these findings suggest that longer dosing intervals should be explored.

Relative bioavailability

The results from Study RB-US-12-0005 (MD) with respect to Subutex and Sublocade Cavg, Cmax and Cmin values are presented in following tables (Table 7 and 8, respectively)

Table 7 Observed steady-state buprenorphine concentrations from lead-in sublingual Subutex before first RBP-6000 injection of 100 and 300 mg dose

Parameter	Statistic	Subutex/ RBP-6000 8mg/ 100mg[1]	Subutex/ RBP-6000 12mg /100mg[2]	Subutex/ RBP-6000 8mg/ 300mg[3]	Subutex/ RBP-6000 12mg/ 300mg[3]	Subutex/ RBP-6000 16mg/ 300mg[3]	Subutex/ RBP-6000 20mg/ 300mg[3]	Subutex/ RBP-6000 24mg/ 300mg[3]
Cavg,ss	N	15	15	3	4	2	2	3
	Mean	1.251	1.707	0.837	1.782	1.666	2.754	2.907
	SD	0.5362	0.5284	0.2888	0.7419	0.8231	1.1887	0.3635
Cmax,ss	N	15	15	3	4	2	2	3
	Mean	3.964	5.350	2.417	4.77	4.265	10.86	8.267
	SD	1.9131	1.7340	1.1794	1.0576	2.1991	4.5821	1.9868
Cmin,ss	N	15	15	3	4	2	2	3
	Mean	0.568	0.806	0.482	0.777	0.763	1.134	1.543
	SD	0.2367	0.3638	0.0854	0.36	0.5056	0.2772	0.2566

1: Cohort 4 Subutex/RBP-6000 8mg/100mg
2: Cohort 2 Subutex/RBP-6000 12mg/100mg
3: Cohort 6 Subutex/RBP-6000 8mg/300mg, 12mg/300mg, 16mg/300mg, 20mg/300mg, 24mg/300mg
SD: standard deviation

Table 8 Observed buprenorphine concentrations after first, fourth and sixth RBP-6000 subcutaneous injections for 100 and 300 mg doses

Parameter	Inj. #	Statistic	Subutex/ RBP-6000 8mg/ 100mg[1]	Subutex/ RBP-6000 12mg/ 100mg[2]	Subutex/ RBP-6000 8mg/ 300mg[3]	Subutex/ RBP-6000 12mg/ 300mg[3]	Subutex/ RBP-6000 16mg/ 300mg[3]	Subutex/ RBP-6000 20mg/ 300mg[3]	Subutex/ RBP-6000 24mg/ 300mg[3]
Cavg,ss	1	N	14	14	1	3	2	2	3
		Mean	0.615	0.687	1.45	1.89	1.76	1.78	2.19
		SD	0.1980	0.2116	.	0.94	0.17	0.13	0.72
	4	N	8	11		2			

		Mean	1.897	1.893		4.81			
		SD	0.3763	0.646		0.64			
Cmax,ss	1	N	15	15	3	4	2	2	3
		Mean	1.686	2.023	3.02	6.06	4.58	4.45	5.37
		SD	0.62	0.8251	0.53	0.79	0.88	0.07	1.79
	4	N	10	12		3	2		2
		Mean	2.554	3.066		9.63	11.07		8.22
		SD	0.4775	0.8658		2.79	1.74		2.48
	6	N				1			
		Mean				7.14			
		SD				.			
Cmin,ss	1	N	15	15	3	4	2	2	3
		Mean	0.41	0.375	0.48	0.73	0.74	1.05	1.25
		SD	0.1955	0.1001	0.09	0.24	0.48	0.16	0.42
	4	N	10	12		3	2		2
		Mean	1.18	1.263		4.45	4.13		3.35
		SD	0.2803	0.3574		0.69	0.52		0.44
	6	N				1			
		Mean				4.29			
		SD				.			

1: Cohort 4 Subutex/RBP-6000 8mg/100mg
2: Cohort 2 Subutex/RBP-6000 12mg/100mg
3: Cohort 6 Subutex/RBP-6000 8mg/300mg, 12mg/300mg, 16mg/300mg, 20mg/300mg, 24mg/300mg
SD: standard deviation

Comparisons of buprenorphine Cavg,ss, C_{max},ss, and Cmin,ss of Sublocade 100 and 300 mg and Subutex SL tablet are presented in Table 9,

Table 10, and Table 11, respectively.

Table 9 Buprenorphine Cavg,ss comparison between 100 and 300 mg RBP-6000 SC injections and "lead-in" Subutex SL tablet daily administration

PK parameter	Subutex SL mg	Steady-state Subutex SL mean	RBP-6000 mg	Inj. #	RBP-6000 SC mean	RBP-6000/Subutex ratio[a]
Cavg,ss	8*	1.251	100	1	0.615	0.513
				4	1.897	1.624
	12#	1.707	100	1	0.687	0.404
				4	1.893	1.114
	8^	0.837[1]	300	1	1.45[4]	1.793
	12^	1.782[2]	300	1	1.89[1]	1.043
				4	4.81[3]	2.848
	16^	1.666[3]	300	1	1.76[3]	1.124
	20^	2.754[3]	300	1	1.78[3]	0.676
	24^	2.907[1]	300	1	2.19[1]	0.726

1: N=3 2: N=4 3: N=2;
*: Cohort 4 Subutex/RBP-6000 8mg/100mg
#: Cohort 2 Subutex/RBP-6000 12mg/100mg
^: Cohort 6 Subutex/RBP-6000 8mg/300mg, 12mg/300mg, 16mg/300mg, 20mg/300mg, 24mg/300mg
a: Geometric mean ratio

Table 10 Buprenorphine Cmax,ss comparison between 100 and 300 mg RBP-6000 SC injections and "lead-in" Subutex SL tablet daily administration

PK parameter	Subutex SL mg	Steady-state Subutex SL mean	RBP-6000 mg	Inj. #	RBP-6000 SC mean	RBP-6000/Subutex ratio[a]
Cmax,ss	8*	3.964	100	1	1.686	0.447
				4	2.554	0.709
	12#	5.350	100	1	2.023	0.366
				4	3.066	0.580
	8^	2.417[1]	300	1	3.02[1]	1.332
	12^	4.77[2]	300	1	6.06[2]	1.286
				4	9.63[1]	2.003
				6	7.14[4]	1.526
	16^	4.265[3]	300	1	4.58[3]	1.141
				4	11.07[3]	2.770
	20^	10.86[3]	300	1	4.45[3]	0.429
	24^	8.267[1]	300	1	5.37[1]	0.634
				4	8.22[3]	0.991

1: N=3 2: N=4 3: N=2 4: N=1
*: Cohort 4 Subutex/RBP-6000 8mg/100mg
#: Cohort 2 Subutex/RBP-6000 12mg/100mg
^: Cohort 6 Subutex/RBP-6000 8mg/300mg, 12mg/300mg, 16mg/300mg, 20mg/300mg, 24mg/300mg
a: Geometric mean ratio

Table 11 Buprenorphine Cmin,ss comparison between 100 and 300 mg RBP-6000 SC injections and "lead-in" Subutex SL tablet daily administration

PK parameter	Subutex SL mg	Steady-state Subutex SL	RBP-6000 mg	Inj. #	RBP-6000 SC mean	RBP-6000/Subutex ratio[a]

		mean				
Cmin,ss	8*	0.568	100	1	0.41	0.723
				4	1.18	2.218
	12#	0.806	100	1	0.375	0.505
				4	1.263	1.687
	8^	0.482[1]	300	1	0.48[1]	1.000
	12^	0.777[2]	300	1	0.73[2]	0.987
				4	4.45[3]	6.199
				6	4.29[4]	6.017
	16^	0.763[3]	300	1	0.74[3]	0.982
				4	4.13[3]	6.107
	20^	1.134[3]	300	1	1.05[3]	0.934
	24^	1.543[1]	300	1	1.25[1]	0.787
				4	3.35[3]	2.186

1: N=3 2: N=4 3: N=2 4: N=1
*: Cohort 4 Subutex/RBP-6000 8mg/100mg
#: Cohort 2 Subutex/RBP-6000 12mg/100mg
^: Cohort 6 Subutex/RBP-6000 8mg/300mg, 12mg/300mg, 16mg/300mg, 20mg/300mg, 24mg/300mg
a: Geometric mean ratio

The observed arithmetic mean Cavg buprenorphine concentrations ranged from approximately 0.62 to 0.69 ng/mL and approximately 1.45 to 2.19 ng/mL for 100 and 300 mg RBP-6000 doses, respectively, after Sublocade Injection 1.

After Sublocade Injection 4, observed steady-state arithmetic mean Cavg buprenorphine concentrations were approximately 1.89-1.9 ng/mL and approximately 4.81 ng/mL (N=2) for 100 and 300 mg RBP-6000 doses, respectively.

Overall, comparing the observed mean buprenorphine concentrations (Cavg) between Sublocade 100 and 300 mg doses to Subutex SL 12 and 24 mg stabilization doses, buprenorphine concentration after Sublocade fourth injection were approximately 11 and 65% higher than that of Subutex 12 and 24 mg, respectively, at steady state. (1.71 vs 1.89 ng/mL and 2.91 vs 4.81 ng/mL, for Subutex vs Sublocade, respectively; Table 12)

Table 12 Overall comparison of buprenorphine mean pharmacokinetic parameters between Subutex and Sublocade after first and fourth subcutaneous injections

Pharmacokinetic parameters	Subutex daily stabilization		RBP 6000			
Mean	12 mg	24 mg	100 mg^ (1st injection)	100 mg^ (4th injection)	300 mg# (1st injection)	300 mg# (4th injection)
$C_{avg,ss}$ (ng/ml)	1.71	2.91	0.69	1.89	2.19	4.81*
$C_{max,ss}$ (ng/ml)	5.35	8.27	2.02	3.01	5.37	9.64*
$C_{min,ss}$ (ng/ml)	0.81	1.54	0.38	1.26	1.25	4.04*

^With Subutex 12 mg stabilization
#With Subutex 24 mg stabilization

*Overall value from Cohort 6-after fourth injection the buprenorphine exposure will be solely from Sublocade injections, as the buprenorphine concentrations from Subutex stabilization phase would not influence the Sublocade bupivacaine exposure, due to 4 months of time lapse since Sublocade first injection.

Furthermore, as a comparison, the estimated steady state buprenorphine Cmax, Cmin, and Cavg from the dosing regimens utilized in Phase 3, 300 mg for first 2 injections followed by four injections of either 300 or 100 mg "maintenance" injections, are presented in Table 13. The Pk parameters of steady state exposure are observed PK data for both 300/300 mg and 300/100 mg regimens. It is noted that in the multiple dose study, RB-US-12-0005, there were a full PK sampling with both 300mg and 100 mg after 4th injection.

Table 13 Observed steady-state pharmacokinetic parameters of buprenorphine (mean (%CV)) for the 300/100 mg and the 300/300 mg dosing regimens of rbp-6000 in study RB-US-13-0001

Dosing Regimen	N	$C_{max,ss}$ (ng/mL)	$C_{min,ss}$ (ng/mL)	$C_{avg,ss}$ (ng/mL)
300/100 mg	102	4.88 (35.0)	2.48 (30.0)	3.21 (25.5)
300/300 mg	102	10.12 (40.4)	5.01 (31.9)	6.54 (31.7)

The Applicant's Response, dated November 10, 2017, to Information Request

Linearity

The results of Study RB-US-11-0020 (SD) indicate that after a single-dose RBP-6000 SC injection ranging from 50 to 200 mg, pharmacokinetic parameters increased at a rate that was less than proportional to dose. The dose proportionality analyses for buprenorphine are presented in Tables 14 and 15.

Table 14 Statistical analysis of dose linearity for buprenorphine from a single dose RBP-6000 50, 100 and 200 mg in Study RB-US-11-0020 (note: Cohort 2: 100 mg)

PK Parameter	**Estimate (beta1)**	**p-value**	**90% CI of Slope**
C_{max} (ng/mL)	0.626	<.001	(0.509, 0.744)
C_{avg} (ng/mL)	0.819	0.014	(0.700, 0.937)
$AUC_{Day\ 1\text{-}29}$ (h*ng/mL)	0.819	0.014	(0.700, 0.937)

CI = confidence interval; h = hour(s); PK = pharmacokinetic
Source: Table 14.2.1.5, Listing 16.2.6.2.1, Listing 16.2.6.2.2, and Listing 16.2.6.2.3

Table 15 Dose proportionality assessment after 50, 100 and 200 mg RBP-6000 SC single dose injection

	Dose			x-fold ratio		
	50 mg	100 mg	200 mg	50 mg 1-fold	100 mg 2-fold	200 mg 4-fold
Cmax (ng/mL)	1.05	1.54	2.43	1.00	1.46	2.31
AUCDay1-29 (hr ng/mL)	248.48	425.13	764.92	1.00	1.71	3.08

AUCinf (hr.ng/mL)	866.19	1557.40	3007.82	1.00	1.80	3.47

The results from Study RB-US-12-0005 (MD) indicated that, with the increase in dose from 50 mg to 300 mg following RBP-6000 Injection 1, and 4, the Cmax and AUCtau for buprenorphine increased at a rate less than dose proportional (associated 90% CI of the slope was not entirely contained in the critical region). The statistical analyses for dose proportionality for Cohorts 1-3 for buprenorphine are presented in Table 16.

Table 16 Statistical analysis of dose linearity for buprenorphine from a multiple dose Sublocade 50 to 300 mg in Study RB-US-12-0005

PK	Injection	Estimate	p-value	90% CI of Slope	Critical Region
C_{max}	1	0.675	<0.001	(0.573, 0.776)	(0.875, 1.125)
	4	0.779	0.003	(0.659, 0.898)	(0.875, 1.125)
AUCtau	1	0.826	0.003	(0.731, 0.922)	(0.875, 1.125)
	4	0.823	0.023	(0.697, 0.950)	(0.875, 1.125)

Efficacy findings:

Study RB-US-13-0001 was a Phase 3, randomized, double-blind, placebo-controlled, multi-center study which assessed the efficacy, safety and tolerability of multiple Sublocade injections over 24 weeks [Treatment 1: Sublocade 300 mg for 6 injections (once every 28 days); Treatment 2: Sublocade 300 mg for 2 injections (followed by 100 mg for 4 injections (once every 28 days)] in treatment-seeking subjects with a diagnosis of moderate or severe OUD. Subjects were inducted onto Suboxone SL film for 3 days, followed by a Suboxone SL film run-in dose-adjustment period (4- to 11-day) to achieve buprenorphine doses ranging from 8 to 24 mg/day. The reader is referred to Clinical Review by Drs. Emily Deng and Feng Li, OND and OTS/OB, respectively.

Study RB-US-13-0002 was a double-blind, placebo-controlled, two of Sublocade 300 mg injections (28-day apart; Day 1 and Day 29) study in non-treatment-seeking subjects with moderate to severe OUD to assess the blockade of hydromorphone's subjective effects. Patients were treated with up to 24 mg Suboxone in the lead-in phase. The reader is referred to Control Substance Staff (CSS) Review by Drs. Alan Trachtenberg and Wei Liu, CSS and OB, respectively.

QT findings

No formal QTc study was conducted in this NDA to establish the effect on QT. However, the exposure (concentration)-response relationship for QT was assessed (nonlinear mixed effects modelling (NONMEM)) by the Applicant using data from 5 clinical studies, including the Phase 3 efficacy study (Study 13-0001). For a complete review of QT analysis, the reader is referred to Dr. Gopichand Gottipati's review. The Applicant reported that the results from the modeling indicated that upper 90% CI is under 10 msec after multiple Sublocade injections, even at 2-fold higher than the proposed dose of 300 mg, and, that Sublocade impact on QT is "insignificant" at

clinically relevant buprenorphine concentrations, after considering for the covariates that may influence HR and QT in patients with OUD.

Pediatrics

The Applicant stated that buprenorphine has an orphan drug designation for the indication of opioid dependence. In support of this, the Applicant submitted the 2002 Suboxone tablet Orphan Status Approval letter dated June 15, 1994, which states that buprenorphine qualified for orphan designation for the treatment of opiate addiction in opiate users under Section 526(a)(2)(B) of the FFDCA (application #93-752). Thus, Sublocade is exempt from the PREA requirements.

Hepatic and renal impairment

No dedicated RBP-6000 pharmacokinetic studies were conducted in hepatically-impaired or renally-impaired patients.

With respect to hepatic impairment, the effect on buprenorphine PK has been previously evaluated with Suboxone sublingual tablets (2 mg/0.5 mg buprenorphine/naloxone) in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria (see Suboxone Film Prescribing Information 2017). The labeling states that "While no clinically relevant changes were observed in subjects with mild hepatic impairment, buprenorphine plasma exposure was increased by 64% and 181% in subjects with moderate and severe hepatic impairment, respectively, compared to healthy subjects." Due to the lack of first-pass effect, the effect of hepatic impairment on pharmacokinetics of RBP-6000 is expected to be less than the effect on Suboxone sublingual film. However, due to lacking of dedicated hepatic impairment study with Sublocade, the magnitude of PK changes in subjects with moderate or severe impairment is unknown.

With respect to renal impairment, the information provided with Suboxone sublingual film was referenced (no differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine), indicating that buprenorphine undergoes hepatic extraction and metabolism and that buprenorphine systemic clearance is not significantly related to renal function.

Geriatric

No dedicated RBP-6000 pharmacokinetic studies were conducted in elderly patients. It is generally accepted that reported clinical experience with buprenorphine has not identified differences in responses between elderly and younger patients. Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in geriatric patients, the decision to should be made cautiously in individuals 65 years of age or older and these patients should be monitored for signs and symptoms of toxicity or overdose (Noted from Subutex Label).

Drug interactions

No dedicated RBP-6000 pharmacokinetic studies were conducted to evaluate drug interactions. Buprenorphine is mainly metabolized via CYP3A4; co-administration of other drugs which are inhibitors or inducers of CYP3A4 activity can affect the pharmacokinetics of RBP-6000. Due to the lack of first-pass effects for RBP-6000, the magnitude of drug interaction with a 3A4 inhibitor or inducer is expected to be less for RBP-6000 in comparison to SL buprenorphine products (See Section 3.3 for discussion). With SL administration, a portion of the dose is typically swallowed.

The effects of co-administered inducers or inhibitors have been established in studies using transmucosal buprenorphine and the effects may be dependent on the route of administration. However, due to lacking of dedicated drug interaction studies with Sublocade and 3A4 inhibitors or inducers, the magnitude of PK changes in subjects with 3A4 inhibitor or inducer is unknown. Since it may not be possible to consider dose adjustment in patients who are on CYP3A4 inhibitors/inducers, the following steps may be necessary and considered for Sublocade.

Patients who transfer to Sublocade treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inhibitors should be monitored to ensure that the plasma buprenorphine level provided by Sublocade is adequate. If patients already on Sublocade require newly-initiated treatment with CYP3A4 inhibitors, the patients should be monitored for signs and symptoms of over- medication. Within 2 weeks of Sublocade administration (due to possibility of remove Sublocade surgically), if the concomitant medication cannot be reduced or discontinued, it may be necessary to remove the Sublocade and treat the patient with a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilized on Sublocade in the setting of concomitant medication that is a CYP3A4 inhibitor, and the concomitant medication is discontinued, the patient should be monitored for withdrawal. If the dose of Sublocade is not adequate in the absence of the concomitant medication, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments.

CYP3A4 inducers may induce the metabolism of buprenorphine and, therefore, may cause increased clearance of the drug which could lead to a decrease in buprenorphine plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome. It is not known whether the effects of CYP3A4 inducers are dependent on the route of administration of buprenorphine. Patients who transfer to Sublocade treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inducers should be monitored to ensure that the plasma buprenorphine level provided by Sublocade is adequate. If patients already on Sublocade require newly-initiated treatment with CYP3A4 inducers, the patients should be monitored for withdrawal. If the dose of Sublocade is not adequate in the absence of the concomitant medication, and the concomitant medication cannot be reduced or discontinued, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilized on Sublocade in the setting of concomitant medication that is a CYP3A4 inducer, and the concomitant medication is discontinued, the patient should be monitored for signs and symptoms of over-medication. Within 2 weeks of Sublocade administration (due to possibility of remove Sublocade surgically), if the dose provided by Sublocade is excessive in the absence of the concomitant inducer, it may be necessary to remove the Sublocade and treat the patient with a formulation of buprenorphine that permits dose adjustments.

It is noted that the Applicant modeled PK following SL Subutex administration and SC injection of RBP-6000 to estimate SL and SC bioavailability parameters, modeled the effect of ketoconazole with separation of first-pass and systemic clearance, and estimated the effect of ketoconazole on PK following RBP-6000 administration. The dataset used to build the model was with Subutex and ketoconazole 400 mg/day. With the model constructed, the Applicant conducted PK simulations to predict the effect of 400 mg ketoconazole per day on buprenorphine exposure following the 4th injection of RBP-6000 100 mg once daily and 300 mg once daily. Four thousand individual AUC values were simulated using the final population parameter values estimated. The Applicant concluded that ketoconazole produces about half the increase in buprenorphine exposure following RBP-6000 administration compared to SL Subutex (e.g. AUC ratio is 2.32 to 2.54 for SL Subutex versus 1.58 to 1.60 for RBP-6000. It is noted that, however, overall, the certainty in the 58%-60% buprenorphine AUC increase due to ketoconazole is not clear, due to uncertainty in the overall modeling assumptions.

Buprenorphine and norbuprenorphine concentration ratio observed in Sublocade

As a SC depot administration, Sublocade avoids the first-pass effect compared to buprenorphine formulations for oral transmucosal administration. The fraction absorbed sublingually of a sublingual buprenorphine product (e.g., Suboxone) also avoids the first-pass effect, whereas the swallowed fraction still undergoes first-pass effect and is metabolized to norbuprenorphine, which will result in a higher exposure ratio of norbuprenorphine to buprenorphine.

Buprenorphine and norbuprenorphine concentrations were measured for both RBP-6000 SC and sublingual Subutex administrations in Study RB-US-11-0005, a multiple dose study. The norbuprenorphine to buprenorphine ratio was much higher for Subutex sublingual lead-in phase compared to RBP-6000 SC 300 mg after the fourth injection. The AUCtau ratio of norbuprenorphine to buprenorphine approximately ranges from 0.23 to 0.39 for RBP-6000 after the fourth injection compared to 1.32 to 3.21 for Subutex sublingual at steady state (RB-US-12-0005). This observation confirms that RBP-6000 undergoes lesser metabolism compared to buprenorphine sublingual product due to lack of first-pass effect.

2.1 Pharmacology and Clinical Pharmacokinetics

2.1.1. What is the proposed indication for Sublocade?

Sublocade contains buprenorphine and is indicated for the treatment of moderate to severe OUD in patients who have undergone stabilization to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine containing product. Sublocade should be used as part of a complete treatment plan to include counselling and psychosocial support. Buprenorphine is a partial agonist at the μ-opioid receptor and an antagonist at the kappa-opioid receptor in the central nervous system. Activation of mu-opioid receptors produce physiological effects of opioids such as pain relief, but also produce the reinforcing and physical dependence of opioids. Buprenorphine

as a partial agonist, it produces a sub-maximal effect compared to that of a full opioid agonist; this may produce lesser degrees of respiratory depression in terms of safety, and, reinforcing and physical dependence of opioid, which, in turn, may provide an effective treatment of OUD.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing for Sublocade

The recommended Sublocade dose, following an stabilization on a transmucosal buprenorphine-containing product, is 300 mg monthly (every 28 days) in the abdominal region ((between the transpyloric and transtubercular planes with adequate subcutaneous tissue that is free of skin conditions (e.g. nodules, lesions, excessive pigment)), and, separated by a minimum of 26 days between doses; the dose may be decreased to 100 mg based upon tolerability. The clinical efficacy of starting treatment with Sublocade 100 mg has not been studied.

A patient who misses a dose of Sublocade should receive the next dose as soon as possible, with the following dose given no less than 26 days later. Unavoidable occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.

Sublocade is for patients who have undergone stabilization on a transmucosal buprenorphine-containing product, e.g., SL tablet, delivering the equivalent of 8 to 24 mg of buprenorphine. The patient may only be transitioned to Sublocade after signs and symptoms of opioid withdrawal have been suppressed for a minimum of 24 hours. Dosing and stabilization of transmucosal buprenorphine-containing products should be based on instructions in their appropriate product label.

2.2.2 Therapeutic individualization

2.2.2.1 Pediatric development iPSP

The Applicant stated that buprenorphine has an orphan drug designation for the indication of opioid dependence. In support of this, the Applicant submitted the 2002 Suboxone tablet Orphan Status Approval letter dated June 15, 1994, which states that buprenorphine qualified for orphan designation for the treatment of opiate addiction in opiate users under Section 526(a)(2)(B) of the FFDCA (application #93-752). Thus, Sublocade is exempt from the PREA requirements.

2.3 Outstanding Issues

There are no outstanding issues at this time.

2.4 Summary of Labeling Recommendations

The labeling review and the labeling changes for this product were conducted. The following recommendations are proposed for Sublocade. As of November 14, 2017, labeling negotiation is still ongoing with the Applicant.

Summary: For Section 12.2, it is recommended that Subutex wording should be used in its entirety for Subjective Effects, Physiologic Effects, and Androgen Deficiency, due to its simplicity (b) (4) [redacted] Additionally there are suggestions provided for Section 12.3 in the following table (Table 17).

Table 17 Labeling comparison and recommendation

Subutex	Proposed Sublocade	Labeling Revision Recommended
--------**WARNINGS AND PRECAUTIONS**---------- □□□SUBUTEX sublingual tablets should be used with caution in patients with moderate to severe hepatic impairment and a dose adjustment is recommended for patients with severe hepatic impairment (5.12)	----**WARNINGS AND PRECAUTION**-------- (b) (4) [redacted]	-No issues – (b) (4) [redacted]
--------**DRUG INTERACTIONS**--------- • Use caution in prescribing SUBUTEX sublingual tablet for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse. (7) • Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing. (7) • Patients who are on chronic buprenorphine treatment should have their dose monitored if NNRTIs are added to their treatment regimen. Monitor patients taking buprenorphine and atazanavir with and without ritonavir, and reduce dose of buprenorphine if warranted (7). • Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue SUBUTEX sublingual tablets if serotonin syndrome is suspected. (7)	---**DRUG INTERACTIONS**---------- (b) (4) [redacted]	-Defer to clinical team; consider adding the following in blue fonts to Sublocade Label from Subutex Label: • Patients who are on chronic buprenorphine treatment should have their dose monitored if NNRTIs are added to their treatment regimen. Monitor patients taking buprenorphine and atazanavir with and without ritonavir, and reduce dose of buprenorphine if warranted (7). -Pending discussion with PM, may have to consider excluding, at least, (b) (4) [redacted] Note: CYP3A4 wording is in Probuphine Label); -No other issues.
----------**USE IN SPECIFIC POPULATIONS**------ • Lactation: Caution should be exercised when administered to a nursing woman. (8.2) • Safety and effectiveness of SUBUTEX sublingual tablet in patients below the age of 16 have not been established. (8.4) • Administer SUBUTEX sublingual tablet with caution to elderly or debilitated patients. (8.5) • SUBUTEX sublingual tablets should be used with caution in patients with moderate to severe hepatic impairment and a dose adjustment is recommended for patients with severe hepatic impairment (8.6)	------USE IN SPECIFIC POPULATIONS---- (b) (4) [redacted]	-Discussion on the following information (b) (4) [redacted] consider adding the following in blue fonts to Sublocade Label: • Lactation: Buprenorphine passes into the mother's milk. (b) (4) [redacted] • (b) (4) [redacted] • (b) (4) [redacted]: Monitor (b) (4) [redacted] for sedation or respiratory depression. (8.5) • Hepatic Impairment: (b) (4) [redacted] NOT

		recommended (b) (4) (8.6)
2.6 Patients with Hepatic Impairment Severe hepatic impairment: Consider reducing the starting and titration incremental dose by half compared to patients with normal liver function, and monitor for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Moderate hepatic impairment: Although no dose adjustment is necessary for patients with moderate hepatic impairment, SUBUTEX sublingual tablets should be used with caution in these patients and prescribers should monitor patients for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Mild hepatic impairment: No clinically significant differences in pharmacokinetic parameters were observed in subjects with mild hepatic impairment. No dose adjustment is needed in patients with mild hepatic impairment [*see Warnings and Precautions (5.12)*].		(b) (4)
5.12 Use in Patients with Impaired Hepatic Function In a pharmacokinetic study, buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. For patients with severe hepatic impairment, a dose adjustment is recommended, and patients with moderate or severe hepatic impairment should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine *[see Dosage and Administration (2.6) and Use in Specific Populations (8.6)]*.	5.11 Use in Patients With Impaired Hepatic Function (b) (4)	-Note: this section very closely resembles Probuphine 5.13 - consider adding the following in blue fonts to Sublocade Label: 5.11 Use in Patients With Impaired Hepatic Function (b) (4) -No other issues.

NO ANNOTATION PROVIDED

7 DRUG INTERACTIONS

Table 3 Includes clinically significant drug interactions with SUBUTEX	
Benzodiazepines	
Clinical Impact	There have been a number of reports regarding coma and death associated with the misuse and abuse of the combination of buprenorphine and benzodiazepines. In many, but not all of these cases, buprenorphine was misused by self-injection of crushed buprenorphine tablets. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists.
Intervention	Closely monitor patients with concurrent use of TRADENAME and benzodiazepines. Warn patients that it is extremely dangerous to self-administer benzodiazepines while taking TRADENAME, and warn patients to use benzodiazepines concurrently with TRADENAME only as directed by their healthcare provider.
Non-Benzodiazepine Central Nervous System (CNS) Depressants	
Clinical Impact	Due to additive pharmacologic effects, the concomitant use of non-benzodiazepine CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and

7 DRUG INTERACTIONS

(b) (4)

7 DRUG INTERACTIONS

- consider adding the following in blue fonts to Sublocade Label
- consider deleting the parts which ~~strikeout~~ was used
- RED fonts are still pending based on discussion with PM team

Benzodiazepines	
(b) (4)	
Clinical Impact	No issues
Intervention	No issues
(b) (4)	

	sedation *[see Warnings and Precautions* (b) (4)
Examples	Alcohol, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids.
Inhibitors of CYP3A4	
Clinical Impact	The concomitant use of buprenorphine and CYP3A4 inhibitors can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of SUBUTEX is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the buprenorphine plasma concentration will decrease [see Clinical Pharmacology (12.3)], potentially resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to buprenorphine.

(b) (4)

Examples	No issues
Inhibitors of CYP3A4	
Clinical Impact	The effects of co-administered CYP3A4 inhibitors on buprenorphine exposure in subjects treated with TRADENAME have not been studied, (b) (4) (b) (4) Patients who transfer to Sublocade treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inhibitors ((b) (4) should be monitored to ensure that the plasma buprenorphine level provided by Sublocade is adequate. If patients already on Sublocade require newly-initiated treatment with CYP3A4 inhibitors, the patients should be monitored for signs and symptoms of over- medication. Within 2 weeks of Sublocade administration, if the concomitant medication cannot be reduced or discontinued, it may be necessary to remove the Sublocade and treat the patient with a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilized on Sublocade in the setting of concomitant medication that is a CYP3A4 inhibitor, and the concomitant medication is

		(b) (4)		discontinued, the patient should be monitored for withdrawal. If the dose of Sublocade is not adequate in the absence of the concomitant medication, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments. (b) (4)
Intervention	If concomitant use is necessary, consider dosage reduction of SUBUTEX until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the SUBUTEX dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.		*Intervention*	No issues
Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)		*Examples*	No issues
			CYP3A4 Inducers	

CYP3A4 Inducers	
Clinical Impact	The concomitant use of buprenorphine and CYP3A4 inducers can decrease the plasma concentration of buprenorphine [see Clinical Pharmacology (12.3)], potentially resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to buprenorphine. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the buprenorphine plasma concentration will increase [see Clinical Pharmacology (12.3)], which could increase or prolong both therapeutic effects and adverse reactions and may cause serious respiratory depression.

(b) (4)

Clinical Impact	The effects of co-administered CYP3A4 inducers on buprenorphine exposure in subjects treated with TRADENAME have not been studied. (b) (4) CYP3A4 inducers may induce the metabolism of buprenorphine and, therefore, may cause increased clearance of the drug which could lead to a decrease in buprenorphine plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome. (b) (4) (b) (4) (b) (4) Patients who transfer to Sublocade treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inducers should be monitored to ensure that the plasma buprenorphine level provided by Sublocade is (b) (4). If patients already on Sublocade require newly-initiated treatment with CYP3A4 inducers, the patients should be monitored for withdrawal. If the dose of Sublocade is not adequate in the absence of the concomitant medication, and the concomitant medication cannot be reduced or discontinued, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilized on Sublocade in the setting of concomitant medication that is a CYP3A4 inducer, and the concomitant medication is discontinued, the patient should be monitored for signs and symptoms of over-medication. Within 2 weeks of Sublocade administration, if the dose provided by Sublocade is excessive in the absence of the concomitant inducer, it may be necessary to remove the Sublocade and treat the patient with a formulation of buprenorphine that

		(b) (4)		permits dose adjustments [see Clinical Pharmacology (12)]. (b) (4)
Intervention	If concomitant use is necessary, consider increasing the SUBUTEX dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider SUBUTEX dosage reduction and monitor for signs of respiratory depression.		*Intervention*	No issues
Examples	Rifampin, carbamazepine, phenytoin		*Examples*	No issues
Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			**Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** (b) (4)	
Clinical Impact	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine, and etravirine are known CYP3A inducers, whereas delaviridine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects.		*Clinical Impact*	-Delete 'SUBLINGUAL' – does not provide additional meaning …Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and ~~SUBLINGUAL~~ buprenorphine have been shown in clinical studies,… No issues
Intervention	Patients who are on chronic SUBUTEX treatment should have their dose monitored if NNRTIs are added to their treatment regimen.		*Intervention*	No issues
Examples	Efavirenz, nevirapine, etravirine, delavirdine			

Antiretrovirals: Protease inhibitors (PIs)	
Clinical Impact	Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on (b) (4) buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine (b) (4) and patients in one study reported increased sedation. Symptoms of opioid excess have been found in postmarketing reports of patients receiving (b) (4) buprenorphine and atazanavir with and without ritonavir concomitantly.
Intervention	Monitor patients taking TRADENAME and atazanavir with and without ritonavir, and reduce dose of SUBUTEX if warranted.
Examples	Atazanavir, ritonavir
Antiretrovirals: Nucleoside reverse transcriptase inhibitors (NRTIs)	
Clinical Impact	Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected.
Intervention	None
Serotonergic Drugs	
Clinical Impact	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.

(b) (4)

Examples	No issues
Antiretrovirals: Protease inhibitors (PIs)	
(b) (4)	
Clinical Impact	No issues
Intervention	(b) (4)
Examples	No issues
Antiretrovirals: Nucleoside reverse transcriptase inhibitors (NRTIs)	
(b) (4)	
Clinical Impact	No issues
Intervention	No issues
Serotonergic Drugs	
(b) (4)	

Intervention	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue SUBUTEX if serotonin syndrome is suspected.	(b) (4)	*Clinical Impact*	No issues
Examples	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).		*Intervention*	No issues Note: Similar wording in Probuphine Label
			Examples	No issues
Monoamine Oxidase Inhibitors (MAOIs)			**Monoamine Oxidase Inhibitors (MAOIs)**	(b) (4)
Clinical Impact	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma).		*Clinical Impact*	No issues
Intervention	The use of SUBUTEX is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.		*Intervention*	No issues
Examples	Phenelzine, tranylcypromine, linezolid		*Examples*	No issues
Muscle Relaxants			**Muscle Relaxants**	(b) (4)
Clinical Impact	Buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.		*Clinical Impact*	No issues
Intervention	Monitor patients receiving muscle relaxants and SUBUTEX for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of SUBUTEX and/or the muscle relaxant as necessary.		*Intervention*	No issues
Diuretics				

Clinical Impact	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact	The concomitant use of anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention	Monitor patients for signs of urinary retention or reduced gastric motility when TRADENAME is used concomitantly with anticholinergic drugs.

(b) (4)

Diuretics	
(b) (4)	
Clinical Impact	No issues
Intervention	No issues
Anticholinergic Drugs	
(b) (4)	
Clinical Impact	No issues
Intervention	No issues

8.4 Pediatric Use
The safety and effectiveness of SUBUTEX sublingual tablet has not been established in pediatric patients.

No issues

8.5 Geriatric Use

Clinical studies of SUBUTEX sublingual tablet, SUBOXONE sublingual film, or SUBOXONE sublingual tablet did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

No issues

(b) (4)

8.6 Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a pharmacokinetic study.

Buprenorphine is extensively metabolized in the liver and buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. For patients with severe hepatic impairment, a dose adjustment is recommended, and patients with moderate or severe hepatic impairment should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. *[see Dosage and Administration (2.5), Warnings and Precautions (5.11) and Clinical Pharmacology (12.3)]*.	(b) (4)	Patients (b) (4) who develop moderate-to-severe hepatic impairment while being treated with TRADENAME should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. If signs and symptoms of toxicity or overdose occur within 2 weeks of Sublocade administration, removal of Sublocade may be required. No other issues (b) (4)
8.7 Renal Impairment No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine.		No issues
12 CLINICAL PHARMACOLOGY **12.1 Mechanism of Action** SUBUTEX sublingual tablet contains buprenorphine, a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor.		Sublocade Injection contain buprenorphine. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. (b) (4)

(b) (4)

(b) (4)

12.2 Pharmacodynamics

Subjective Effects

Comparisons of buprenorphine to full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

Opioid agonist ceiling-effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. Both active drugs produced typical opioid agonist effects. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administration. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

(b) (4)

Physiologic Effects

Physiologic Effects

Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3-hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed. The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree. Androgen Deficiency Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.	(b) (4)	Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O2 saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3-hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed. The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O2 saturation to the same degree. Androgen Deficiency Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

	(b) (4)	
12.3 Pharmacokinetics		12.3 Pharmacokinetics ~~The pharmacokinetics (PK) of buprenorphine following subcutaneous injection of TRADENAME was evaluated in subjects with opioid use disorder after single doses (50 mg to 200 mg) and repeated doses (50 to 300 mg) separated by 28 days for up to 12 injections.~~

	(b) (4)	(b) (4)
Absorption Plasma levels of buprenorphine increased with the sublingual dose of SUBUTEX sublingual tablet (**Table 4**). There was wide inter-patient variability in the sublingual absorption of buprenorphine, but within subjects the variability was low. Both C_{max} and AUC of buprenorphine increased in a linear fashion with the increase in dose (in the range of 4 to 16 mg), although the increase was not directly dose-proportional.		Absorption After Sublocade injection, an initial buprenorphine peak was observed and the median Tmax occurred at 24 hours after injection. After the initial buprenorphine peak, the plasma buprenorphine concentrations decreased slowly (b) (4)
Distribution Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.		No issues
Excretion ***Metabolism*** Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it (b) (4)		(b) (4)

(b) (4)

Elimination

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

(b) (4)

, buprenorphine has a mean elimination half-life from plasma ranging from 31 to 35 hours.

(b) (4)

(b) (4)

Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity.

Excretion

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of the buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

(b) (4)

Drug Interactions Studies:

CYP3A4 Inhibitors and Inducers

Subjects receiving SUBUTEX sublingual tablet should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving SUBUTEX sublingual tablet be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered *[see Drug Interactions (7)]*.

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine has been found to be a moderate CYP2D6 inhibitor in in vitro studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and

(b) (4)

CYP3A4 Inhibitors and Inducers

The effects of co-administered CYP3A4 inhibitors and inducers on buprenorphine exposure in subjects treated with TRADENAME have not been studied.

(b) (4)

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its

norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.	(b) (4)	major metabolite, norbuprenorphine has been found to be a moderate CYP2D6 inhibitor in in vitro studies employing human liver microsomes. However, the (b) (4) plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to (b) (4) .
		(b) (4)
	(b) (4)	
		(b) (4)

(b) (4)

Specific Populations

Hepatic Impairment

In a pharmacokinetic study, the disposition of buprenorphine was determined after administering a 2.0/0.5 mg SUBOXONE (buprenorphine (b) (4) naloxone) sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine in patients with hepatic impairment was compared to disposition in subjects with normal hepatic function.

In subjects with mild hepatic impairment, the changes in mean Cmax, AUC0-last, and half-life values of buprenorphine were not clinically significant. No dose adjustment is needed in patients with mild hepatic impairment.

For subjects with moderate and severe hepatic impairment, mean Cmax, AUC0-last, and half-life values of buprenorphine were increased (Table 5). *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.6)]*.

Table 5 Changes in Buprenorphine Pharmacokinetic Parameters in Subjects with Moderate and Severe Hepatic Impairment

Hepatic Impairment	PK Parameters	Increase in buprenorphine compared to healthy subjects
Moderate	C_{max}	8%
	$AUC_{0\text{-last}}$	64%
	Half-life	35%
Severe	C_{max}	72%
	$AUC_{0\text{-last}}$	181%
	Half-life	57%

Specific Populations

(b) (4)

Hepatic Impairment

(b) (4)

The effect of hepatic impairment on the PK of Sublocade has not been (b) (4) . However, the effect of hepatic impairment on the PK of buprenorphine has been evaluated in a study using 2 mg/0.5 mg buprenorphine/naloxone sublingual tablet in subjects with various degrees of hepatic impairment as indicated by Child-Pugh criteria.

While no clinically relevant changes were observed in subjects with mild hepatic impairment, buprenorphine plasma exposure was increased by 64% and 181% in subjects with moderate and severe hepatic impairment, respectively, compared to healthy subjects.

(b) (4)

	(b) (4)	*Renal Impairment* Clinical studies of Sublocade did not include subjects with severe renal impairment. (b) (4) ~~Less than 1% is excreted as unchanged buprenorphine in urine following IV buprenorphine administration.~~ No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine. (b) (4) (b) (4)
HCV infection In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean Cmax, AUC0-last, and half-life values of buprenorphine were not clinically significant in comparison to healthy subjects without HCV infection. No dose adjustment is needed in patients with HCV infection.		Include: *HCV infection* In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean Cmax, AUC0-last, and half-life values of buprenorphine were not clinically significant in comparison to healthy subjects without HCV infection. No dose adjustment is needed in patients with HCV infection.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

3.1.1 What is Sublocade?

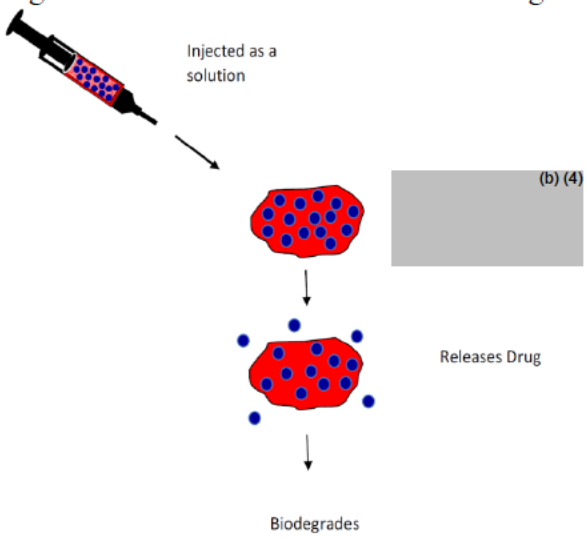
Sublocade is an extended-release sterile product with buprenorphine in the ATRIGEL® Delivery System. Sublocade is supplied in a prefilled syringe in dosage strengths of 100 mg and 300 mg of buprenorphine base and is subcutaneously (SC) injected in the abdominal region. Sublocade is designed to deliver buprenorphine over a minimum of 28 days after subcutaneous injection (Figure 1).

Upon SC injection, Sublocade forms a semi-solid depot (Figure 2) that releases buprenorphine via diffusion as the ATRIGEL polymer biodegrades. The ATRIGEL Delivery System is a non-aqueous solution composed of 1) a biodegradable 50:50 poly(DL-lactide-coglycolide) polymer (PLGH)((b) (4) and, 2) N-methyl-2-pyrrolidone (NMP)(a

biocompatible solvent, [redacted] (b) (4) . The overall process involves a formation of semi-solid depot at the injection site [redacted] (b) (4) and, finally, releasing of buprenorphine from the depot by diffusion.

The ATRIGEL Delivery System has been used in several approved products, including Eligard® products (subcutaneous [SC] depot formulations of leuprolide acetate for palliative treatment of advanced prostate cancer), Atridox® (doxycycline hyclate applied to the periodontal pocket for chronic periodontal disease), the Atrisorb® Bioabsorbable Guided Tissue Regeneration Barrier for periodontal application, and the Atrisorb-D Barrier (Atrisorb with doxycycline) for periodontal guided tissue regeneration.

Figure 1 Overview of the ATRIGEL Drug Delivery Technology

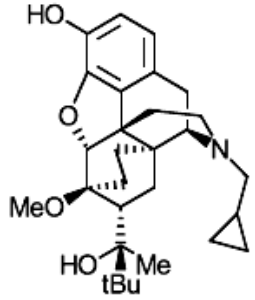


(b) (4)

Physical characteristics of buprenorphine:

Buprenorphine (Figure 3) is a non-hydrogroscopic white to pale cream powder. Buprenorphine has an intrinsic (aqueous) solubility of 6.95 µg/mL, is very slightly soluble in water (0.1-1 mg/mL), freely soluble in acetone (100-1000 mg/mL), soluble in methanol (33.3-100 mg/mL), slightly soluble in cyclohexane (1-10 mg/mL) and very soluble in N-methyl-2-pyrrolidone (NMP) (>1000 mg/mL). Chemical formula is $C_{29}H_{41}NO_4$. Molecular mass is 467.6. Melting point is 218°C (onset by Differential Scanning Calorimetry (DSC)). Buprenorphine pKa's are 9.8 (acid) and 8.6 (base), and, partition coefficient is 5.38 (LogP). Buprenorphine has a (b) (4) .

Figure 3 Buprenorphine structural formula



3.1.2 What are the highlights of Sublocade clinical development plan?

The Applicant stated that Sublocade clinical program was based on the development of an extended release formulation which delivers clinically relevant buprenorphine concentrations for at least 28 days without need for supplemental buprenorphine, e.g., "rescue" sublingual buprenorphine, while preventing any related safety concerns high buprenorphine concentrations for treatment of moderate to severe OUD in patients who have undergone stabilization to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. The Applicant stated in the submission that the most effective treatment of OUD is centered on the prevention of withdrawal symptoms and craving (Childress 1986) and the prevention of the use of illicit opioids. The Applicant stated further that the suppression of opioid withdrawal appears to require >50% brain mu-opioid receptor occupancy (buprenorphine trough plasma concentrations of >1 ng/mL; Greenwald 2014), and, that the suppression of subjective drug-liking effects (opioid blockade) of full agonist-induced responses appears to require ≥70% brain mu-opioid receptor occupancy (buprenorphine plasma concentrations of ≥2 ng/mL). Based on the literature information (Greenwald 2007), the Applicant stated that, although sublingual buprenorphine achieves the 2 ng/mL threshold concentration, this threshold concentration is not maintained over the 24-h dosing interval, e.g., for daily doses of sublingual buprenorphine 16 mg, mu-opioid receptor occupancy was reported to be approximately 70% at 4 h post-dose and only 46% at 28 h post-dose. In all, Sublocade was developed to deliver buprenorphine that would attain and sustain plasma concentrations >2 ng/mL over the entire treatment period. The Applicant recommends that Sublocade should be used as part of a complete treatment plan to include counselling and psychosocial support related to OUD.

(b) (4)

Sublocade will be administered at a physician's office or at a clinical treatment center, which will further minimize the potential for diversion. Misuse and diversion continue to be an issue with current daily treatment of buprenorphine.

There are some approved buprenorphine products on the market for the treatment of opioid dependence. Most are sublingual formulations: Suboxone (buprenorphine HCl/naloxone HCl) buccal/sublingual film/tablet, Bunavail (buprenorphine HCl/naloxone HCl) buccal film, Zubsolv (buprenorphine HCl/naloxone HCl) sublingual tablet. At start of the treatment period the patients initially start with stabilization, preferably with single entity buprenorphine, e.g., Subutex, followed by combination product with buprenorphine and naloxone (mu-opioid receptor antagonist), e.g., Suboxone. The starting stabilization dose may be selected based on the type of illicit opioid drugs being used, e.g., long- or short-acting. Patients are titrated up- or downwards until the maintenance SL dose is achieved. Similar to Sublocade, Probuphine (buprenorphine HCl) is an implantation product, which 4 rods are surgically implanted subdermally for a period of 6 months; the rods are removed after 6 months promptly. Probuphine is indicated for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product. Specifically, Probuphine is only for the patients who are stabilized on doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet or generic equivalent. If Sublocade

is approved, it would be the first once-monthly injectable solution buprenorphine product indicated for the treatment of OUD.

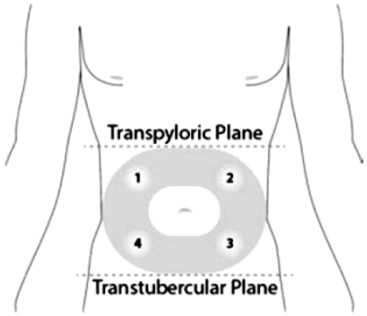
3.1.3 What is the proposed route of Sublocade administration?

Sublocade is proposed to be administered via subcutaneous injection in the abdominal region, and, must not be administered intravenously or intramuscularly. The usual adult dosage is one injection, 300 mg buprenorphine, every 28 days in patients who were stable on a transmucosal buprenorphine-containing product. The dose may be decreased to 100 mg based upon tolerability; however, the clinical efficacy of initiating treatment with Sublocade 100 mg has not been studied. Sublocade should only be prepared and administered by a healthcare provider. A patient who misses a dose should receive the next dose as soon as possible, with the following dose given no less than 26 days later. Unavoidable occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.

Sublocade should be injected in the abdomen region between the transpyloric and transtubercular planes with adequate subcutaneous tissue that is free of skin conditions (e.g. nodules, lesions, excessive pigment). The subject should be in the supine position and do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred in any way. The injection sites should be rotated to avoid skin irritation (Figure 4).

Figure 4 Sublocade injection sites

Figure 4



3.1.4 Sublocade formulation

The list of all Sublocade ingredients, function and reference to quality standards in the drug product are provided in Table 18.

Table 18 List of ingredients for RBP-6000

Component	Function	Reference to quality standard
Buprenorphine	API	Ph. Eur.
50:50 Poly(DL-lactide-co- glycolide) (PLGH)	(b) (4)	In-House

N-methyl-2-pyrrolidone (NMP)	Solvent	Ph. Eur.a
(b) (4)		

API Active Pharmaceutical Ingredient
US-NF United States-National Formulary
Ph. Eur. European Pharmacopoeia
a Pharmaceutical Grade

(b) (4)

Sublocade is formulated in two strengths, 100 mg and 300 mg. Table 19 provides drug product composition per 100 and 300 mg unit.

Table 19 Nominal Composition of Delivered RBP-6000 Drug Product

Component	Nominal (% w/w)	100 mg Syringe (mg)	300 mg Syringea (mg)
Buprenorphine	18	100	300
50:50 Poly(DL-lactide-co-glycolide)	(b) (4)	178	533
N-methyl-2-pyrrolidone		278	833
(b) (4)			
Approximate Delivered Volume (mLb)	-	0.5	1.5

a Delivered mass does not equal the sum of the components due to rounding
b Approximate volume based on the (b) (4)

(b) (4)

3.1.5 What are the highlights of the Sublocade pharmaceutical development plan?

Significant Manufacturing process development:
For the initial clinical trial, RBP-6000 Lot 111 was manufactured per the "Process 1" (b) (4)

Phase 2 clinical RBP-6000 Lots 132 and 133 were manufactured by Modified Process 1 (b) (4)

For late Phase 1 RBP-6000 clinical Lots 161 and 162 Manufacturing "Process 2" (b) (4) was utilized. All processes were conducted (b) (4). The commercial formulation was used in all clinical trials and in the manufacture of the registration batches.

Discussion on molecular weight of PLGH polymer in Sublocade formulation

(b) (4)

(b) (4). A comparative bioavailability study (Study RB-US-13-0006) was conducted to assess the buprenorphine exposure of Sublocade formulated with different MW of PLGH, namely, from 9 kDa to 17 kDa MW of PLGH. The MW range evaluated in Study RB-US-13-0006 covered the formulations used in other clinical studies, including the pivotal Phase 3 trial, RB-US-13-0001 ((b) (4) kDa) (Figure 5). It is noted that, however, Study RB-US-13-0006 did not assesse (b) (4) kDa, (b) (4) and, no explanation was provided in the Application with respect to why the Applicant did not assess (b) (4)

Figure 5 Molecular weight range used in clinical studies

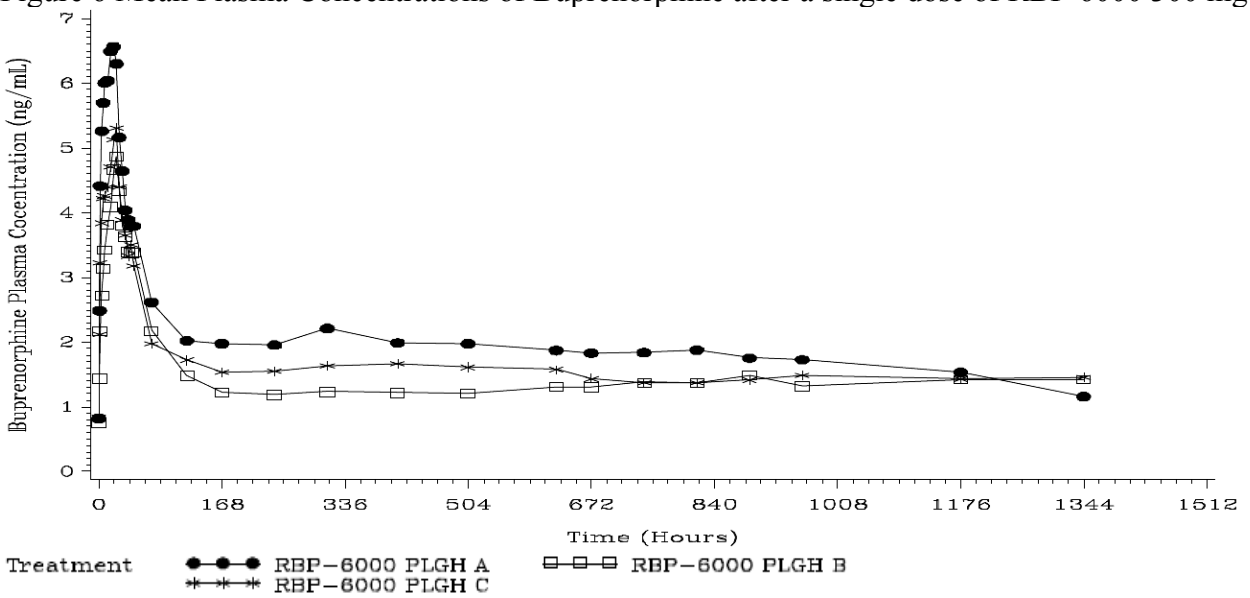
Drug Product		Clinical Study		Molecular Weight (kDa)
Product Lot Number	Dose Strength (mg)	Descriptor	Number	(b) (4)
158	100	Ph3 Efficacy	RB-US-13-0001	
160	300	Ph3 Efficacy	RB-US-13-0001	
184	300	Ph3 Efficacy	RB-US-13-0001	
186	100	Ph3 Safety	RB-USD-13-0003	
184	300	Ph3 Safety	RB-USD-13-0003	
196	300	Ph3 Safety	RB-USD-13-0003	
184	300	MW - PK	RB-US-13-0006	
161	300	MW - PK	RB-US-13-0006	
162	300	MW - PK	RB-US-13-0006	
133	300	Opioid Blockade	RB-US-13-0002	
133	NA	MAD	RB-US-12-0005	
132	NA	SAD	RB-US-11-0020	

Source: Response to clinical request; submission dated 9/18/17

Study RB-US-11-0006 was a single-center, randomized, open-label, single-dose, parallel-group study in subjects with OUD who have undergone buprenorphine sublingual stabilization (final stabilized Suboxone film dose of 12 mg) or "lead-in" phase. This study evaluated pharmacokinetics of single dose of RBP-6000 300 mg formulated with three different PLGH MW polymers: 9 kDa of PLGH polymer (RBP-6000 PLGH A; test arm), 14 kDa of PLGH polymer (RBP-6000 PLGH C; reference arm), and, 17 kDa of PLGH polymer (RBP-6000 PLGH B, test arm). Blood samples were collected for the assessment of buprenorphine and norbuprenorphine pharmacokinetics at the following time points: pre-dose, 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44 h post dose, Day 3 through Day 57 at 48, 72, 120, 168, 240, 312, 408, 504, 624, 672, 744, 816, 888, 960, 1176, and 1344 h post dose.

Buprenorphine peak levels were observed approximately 17 h post administration (Figure 6). Buprenorphine pharmacokinetic parameters are presented in Table 20. For the 300 mg dose, the observed mean buprenorphine plasma half-life was 908 h (SD 157 h; note: parameter was represented by only 2 values), corresponding to approximately 38 days. The long half-life is mainly determined by the continuous absorption from RBP-6000 and does not reflect the real elimination half-life of buprenorphine.

Figure 6 Mean Plasma Concentrations of Buprenorphine after a single dose of RBP-6000 300 mg



PLGH A: RBP-6000 300 mg buprenorphine formulated with 9 kDa PLGH polymer (test treatment), subcutaneous (SC) injection
PLGH B: RBP-6000 300 mg buprenorphine formulated with 17 kDa PLGH polymer (test treatment), SC injection
PLGH C: RBP-6000 300 mg buprenorphine formulated with 14 kDa PLGH polymer (reference treatment), SC injection
Source: rbus130006-body.pdf; Figure 11-1; End-of-Text Figure 14.2.1.3.

Table 20 Single-dose RBP-6000 300 mg pharmacokinetic parameters

Parameter		RBP-6000 PLGH A (9 kDa)	RBP-6000 PLGH B (17 kDa)	RBP-6000 PLGH C (14 kDa)
Cmax (ng/mL)	n	16	15	16
	Mean	7.40	5.07	5.93
	SD	2.550	1.734	1.603
AUC0-28days (h*ng/mL)	n	13	13	13
	Mean	1550	1040	1230
	SD	512.7	310.0	422.9
AUClast (h*ng/mL)	n	16	15	16
	Mean	2140	1730	1830
	SD	1140	864.9	941.5
Tmax (h)	n	16	15	16
	Minimum	4.00	12.0	4.00
	Median	16.0	20.0	20.0
	Maximum	24.0	28.0	24.0
Hour 312 (Day 14) (ng/mL)	n	13	13	13
	Mean	2.21	1.23	1.64
	SD	0.73	0.45	0.75
Hour 504 (Day 22) (ng/mL)	n	13	13	13
	Mean	1.97	1.21	1.61
	SD	0.66	0.48	0.56
Hour 672 (Day 29) (ng/mL)	n	13	13	13
	Mean	1.83	1.30	1.43
	SD	0.68	0.62	0.47

RBP-6000 PLGH A: RBP-6000 300 mg buprenorphine formulated with 9 kDa PLGH polymer (test treatment), subcutaneous (SC) injection
RBP-6000 PLGH B: RBP-6000 300 mg buprenorphine formulated with 17 kDa PLGH polymer (test treatment), SC injection
RBP-6000 PLGH C RBP-6000 300 mg buprenorphine formulated with 14 kDa PLGH polymer (reference treatment), SC injection

Hour 312, 504, 672: Table 14.2.2 Summary of plasma concentration of buprenorphine (RBP-6000 phase) Pharmacokinetic set
Source: rbus130006-body.pdf; End-of-Text Table 14.2.6.

The statistical analysis of plasma PK parameters of buprenorphine is presented in Table 21.

Table 21 Statistical Analysis of Plasma Pharmacokinetic Parameters of Buprenorphine (RBP-6000 Phase) (Pharmacokinetic Set)

Parameter (Unit)	Treatment[a]	N	Geometric LS Means	Treatment Comparisons	Ratio of Geometric LS Means (%)	90% CI of Ratio (%)
$AUC_{0\text{-}28days}$ (ng•h/mL)	A	13	1490	A/C	127.097	(103.798, 155.626)
	B	13	993	B/C	84.587	(69.080, 103.574)
	C	13	1170	·	·	·
C_{max} (ng/mL)	A	16	6.98	A/C	122.133	(100.561, 148.333)
	B	15	4.81	B/C	84.190	(69.097, 102.579)
	C	16	5.72	·	·	·
$AUC_{0\text{-}last}$ (ng•h/mL)	A	16	1680	A/C	114.775	(70.271, 187.465)
	B	15	1410	B/C	96.517	(58.616, 158.927)
	C	16	1470	·	·	·

Abbreviations: CI, confidence interval; LS, least squares; NC, not calculated.
Note: An analysis of variance was performed with the natural log-transformed pharmacokinetic parameters as the dependent variable, treatment as fixed effects.
a RBP-6000 PLGH A: RBP-6000 300 mg buprenorphine formulated with 9 kDa PLGH polymer (test treatment), subcutaneous (SC) injection
RBP-6000 PLGH B: RBP-6000 300 mg buprenorphine formulated with 17 kDa PLGH polymer (test treatment), SC injection
RBP-6000 PLGH C: RBP-6000 300 mg buprenorphine formulated with 14 kDa PLGH polymer (reference treatment), SC injection
Source: End-of-Text Table 14.2.9.

RBP-6000 PLGH A Cmax was 22.1% higher compared with RBP-6000 PLGH C. RBP-6000 PLGH A AUC0-28days and AUC0-last were 27.1% and 14.8% higher, respectively, compared with RBP-6000 PLGH C. RBP-6000 PLGH B Cmax was 15.8% lower compared with RBP-6000 PLGH C. RBP-6000 PLGH B AUC0-28days and AUC0-last were 15.4% and 3.48% lower, respectively, compared with RBP-6000 PLGH C. The 90% CIs of the ratios fell outside 80 to 125% for both test treatments (RBP-6000 PLGH A vs. RBP-6000 PLGH C and RBP-6000 PLGH B vs. RBP-6000 PLGH C) indicating that 9 and 17 kDa formulations are not bioequivalent to 14 kDa formulation.

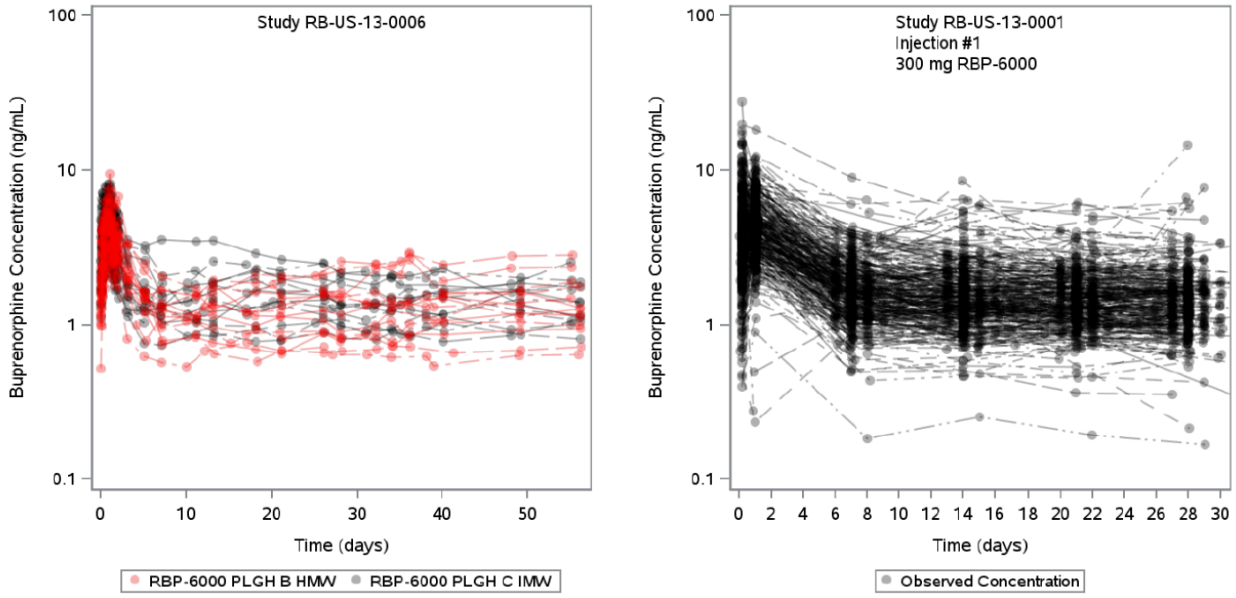
Discussion on buprenorphine exposures from 9 kDa and 17 kDa MW formulation

In Phase 3 trials, the MW PLGH formulation ranges used were (b) (4) kDa (RB-US-13-0001 efficacy: (b) (4) kDa; RB-US-13-0001 safety: (b) (4) kDa). In the Application, the Applicant stated that there are no safety concerns due to higher buprenorphine exposure with low PLGH MW formulation. For high PLGH MW formulation, however, the Applicant did not specify any efficacy concerns due to lower buprenorphine exposure. During the Application review, the Applicant was requested to discuss any rationale(s) that they may have on why the lower

buprenorphine exposure with high PLGH MW formulation is not of concern related to efficacy, as well as higher buprenorphine exposure with low PLGH MW formulation is not of concern related to safety. In response to the request, the Applicant provided responses using the 'intermediate' PLGH MW formulation. It is fair to state that the (b) (4) is a representative formulation utilized in Phase 3 trial.

In the Applicant's response, they acknowledged that average plasma concentrations of buprenorphine following administration of the high PLGH MW formulation are lower than for the intermediate PLGH MW formulation over the first 28 days. Comparing the individual buprenorphine exposure profiles in Study RB-US-11-0006, there is an overlap in buprenorphine plasma concentrations (Figure 7). Although as a cross study comparison, the similar findings are presented from the observed individual buprenorphine profiles (following the Sublocade Injection 1) from the Phase 3 efficacy study (RB-US-13-0001), which demonstrated efficacy in OUD subjects. In all, the Applicant presented that concentrations obtained following administration of the high PLGH MW formulation will not result in lack of efficacy compared to the intermediate PLGH MW formulation.

Figure 7 Individual plasma concentration-time profiles of buprenorphine following Sublocade formulated with high or intermediate molecular weight of PLGH in Study RB-US-13-0006, Compared to Data in the Phase 3 Efficacy Study 13-0001 (First Injection)

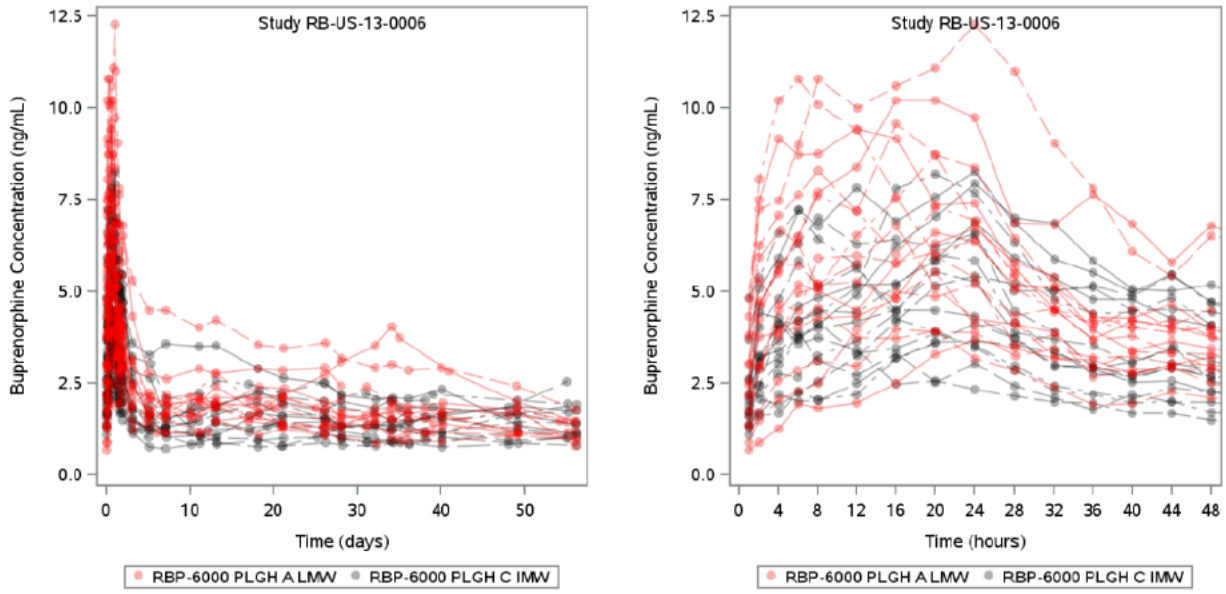


HMW: high molecular weight (red); IMW: intermediate molecular weight (black)
Source: SDTM datasets from Studies 13-0006 and 13-0001; Source: Response to clinical request; submission dated 9/18/17

Similarly, the Applicant acknowledged that average plasma concentrations of buprenorphine following administration of the low PLGH MW formulation are higher than for the intermediate PLGH MW formulation over the first 28 days (Figure 7 above). Comparing the individual buprenorphine exposure profiles in Study RB-US-11-0006, most of the buprenorphine plasma

concentrations profiles overlapped between low and intermediate PLGH MW formulations (Figure 8). For subjects who showed higher buprenorphine exposures, the Applicant compared the observed levels with sublingual buprenorphine 24 and 32 mg exposure information, which Cmax values were 11.9 and 18.1 ng/mL, respectively (Study CSR CR96/008, Protocol 1009; Table 12b; Listing of PK Parameters: Tablet Formulation; Source: Table 16 Comparison of buprenorphine mean PK parameters between RBP-6000 (100 and 300 mg) and SL buprenorphine formulations (8-24 mg); summary-clin-pharm.pdf, m2). In all the Applicant presented that concentrations obtained following administration of the low PLGH MW formulation will not result in safety concerns compared to the intermediate PLGH MW formulation.

Figure 8 Individual plasma concentration-time profiles of buprenorphine following Sublocade formulated with low or intermediate molecular weight of PLGH in Study RB-US-13-0006 over a time period of 56 days (left) and the first 2 days (right)



LMW: low molecular weight (red); IMW: intermediate molecular weight (black)
Source: SDTM datasets from Study 13-0006; Source: Response to clinical request; submission dated 9/18/17

3.2 General Pharmacology and Pharmacokinetic Characteristics

3.2.1 What are the proposed mechanism(s) of actions and known clinical pharmacology information for buprenorphine?

The following information has been obtained from Subutex/Suboxone Labels with respect to buprenorphine. [Source: Subutex (N020732; 9/7/17)]
Buprenorphine (b) (4) a partial agonist at the μ-opioid receptor and an antagonist at the kappa-opioid receptor (b) (4)

(b) (4)

Opioid agonist ceiling-effects were observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, there was a dose that produced no further effect. Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O2 saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3-hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed. The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O2 saturation to the same degree.

Distribution

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Excretion

Metabolism

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it is not known whether norbuprenorphine contributes to the overall effect of (b) (4).

Elimination

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Buprenorphine has a mean elimination half-life from plasma ranging from 31 to 35 hours (b) (4)

Drug Interactions Studies:

CYP3A4 Inhibitors and Inducers

Subjects receiving *buprenorphine* sublingual tablet should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving *buprenorphine* sublingual tablet be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine has been found to be a moderate CYP2D6 inhibitor in in vitro studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

Specific Populations

Hepatic Impairment

In a pharmacokinetic study, the disposition of buprenorphine was determined after administering a 2.0/0.5 mg *buprenorphine with naloxone* sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine in patients with hepatic impairment was compared to disposition in subjects with normal hepatic function.

In subjects with mild hepatic impairment, the changes in mean Cmax, AUC0-last, and half-life values of buprenorphine were not clinically significant. No dose adjustment is needed in patients with mild hepatic impairment.

For subjects with moderate and severe hepatic impairment, mean Cmax, AUC0-last, and half-life values of buprenorphine were increased (*Table 5*).

Table 5 Changes in Buprenorphine Pharmacokinetic Parameters in Subjects with Moderate and Severe Hepatic Impairment

Hepatic Impairment	PK Parameters	Increase in buprenorphine compared to healthy subjects
Moderate	Cmax	8%
	AUC0-last	64%
	Half-life	35%
Severe	Cmax	72%
	AUC0-last	181%
	Half-life	57%

(Note: in addition to Subutex Label information, the following information is from Suboxone Label: The difference in magnitude of the effects on naloxone and buprenorphine are greater in subjects with severe hepatic impairment than subjects with moderate hepatic impairment, and therefore the clinical impact of these effects is likely to be greater in patients with severe hepatic impairment than in patients with moderate hepatic impairment. Buprenorphine/naloxone products

should be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.

HCV infection
In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean Cmax, AUC0-last, and half-life values of buprenorphine were not clinically significant in comparison to healthy subjects without HCV infection. No dose adjustment is needed in patients with HCV infection.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical and clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

See Table 1 above (Section 2) for the clinical studies conducted with Sublocade. Studies, RB-US-11-0020 (SAD), RB-US-12-0005 (MD), RB-US-13-0006 (SD MW), RB-US-13-0002 (Phase 2 SD opioid blockade; administered 2 injections), RB-US-13-0001 (Phase 3 MD up to 6 Sublocade injections were administered) and RB-US-13-0003 (P3 safety extension) were assessed for buprenorphine release profile from Sublocade injection. Out of the 6 studies, Studies RB-US-12-0005 and RB-US-13-0001/0003 were multiple dose studies with buprenorphine SL lead-in phase. Studies RB-US-13-0002 and RB-US-13-0001 were pivotal to support efficacy. The following section, 3.3.2 provides details to Studies RB-US-13-0002 and RB-US-13-0001. In Study RB-US-13-0002 the findings indicated that two injections of 300 mg Sublocade demonstrated blockade of drug-liking of 6 mg hydromorphone and 18 mg hydromorphone. Study RB-US-13-0001 results indicated that both treatments, Sublocade 300 mg for 6 injections and Sublocade 300 mg for 2 injections followed by 100 mg for 4 injections, were efficacious in treating patients with OUD.

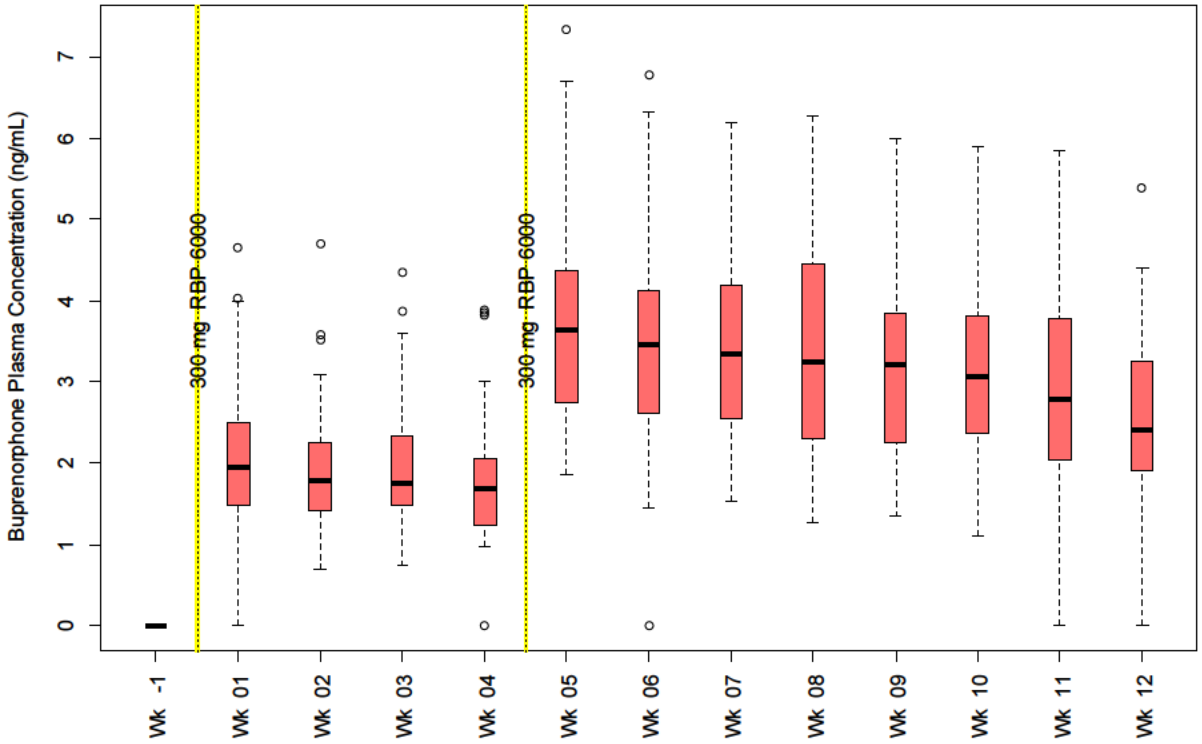
Reviewer analyses of blockade data from study 13-0002: The review team expressed concerns regarding the conduct of Study 13-0002 (please refer to the AC presentation by the C_{SS} reviewer and Statistics reviewer for additional information). One relevant concern was that the mean drug-liking score over a 300-minute testing session was used in statistical analyses. The review team decided that the maximum drug liking score within the 300-minute testing session was the more appropriate measure. As such, the FDA Statistics reviewer re-analyzed the Applicant's data using the maximum (E_{max}) drug-liking scores. Similarly, OCP conducted pharmacokinetic-pharmacodynamic (PKPD) analyses to assess the relationship between the E_{max} drug liking score and buprenorphine exposure following RBP-6000 administration. These PKPD analyses were performed to provide additional context to the statistical issues identified during the review of the blockade study.

PK and PD data were available from n=38 subjects in the blockade study 13-0002 study. The blockade study assessed the effect of buprenorphine on the measure of how much a subject "likes" hydromorphone. Each week there was a hydromorphone testing session where a single intramuscular injection of hydromorphone (0, 6, or 18 mg) was administered once per day for 3 consecutive days in a blinded randomized manner. One hydromorphone session was conducted in

the absence of buprenorphine and 12 hydromorphone sessions, once session per week for 12 weeks, were administered after subjects initiated treatment with SC RBP-6000. RBP-6000 300 mg was administered prior to the Week 1 hydromorphone session and prior to the Week 5 hydromorphone session (2 injections spaced 4 weeks apart). Please refer to Section 2 of this review for additional information on study 13-0002.

PK data were buprenorphine plasma concentrations measured immediately before the hydromorphone challenge. The figure below (Figure 9) shows the distribution of buprenorphine plasma concentrations at each week where SC RBP-6000 300 mg was administered 4 days prior to the hydromorphone challenge sessions at Week 1 and at Week 5.

Figure 9 Distribution of Buprenorphine Concentration Measured Immediately Prior to Hydromorphone Session by Week

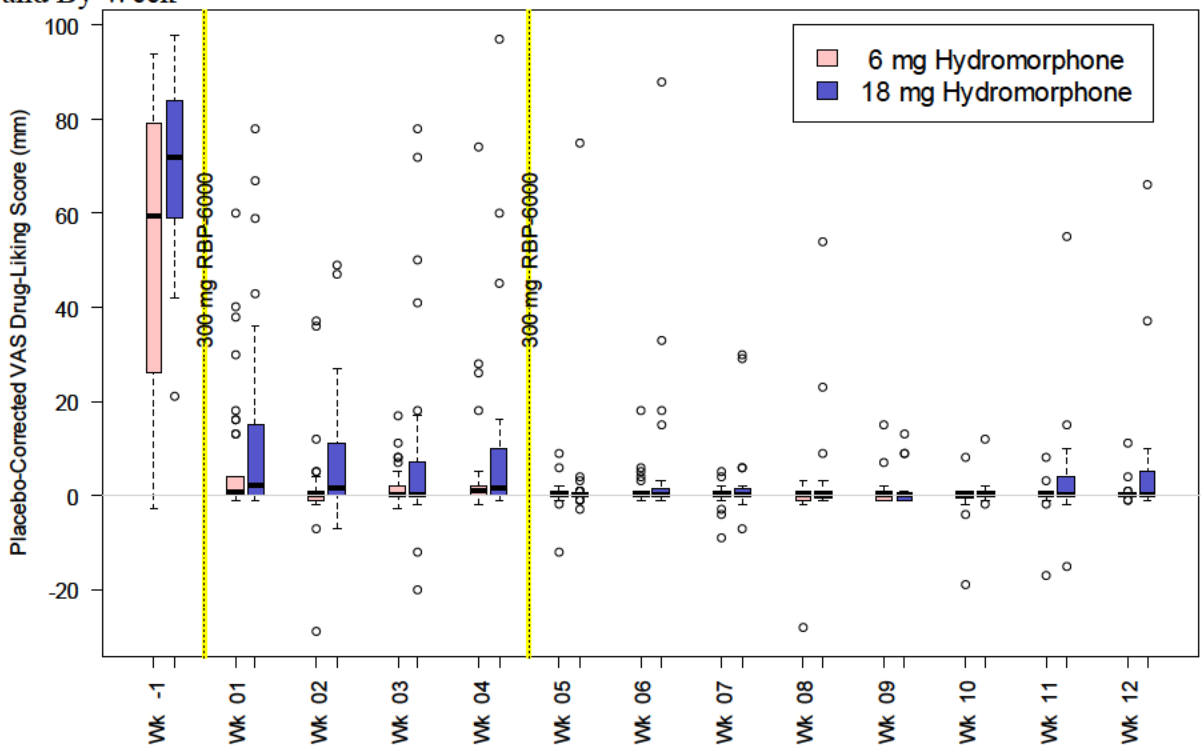


**Vertical yellow lines indicate the timing of SC injections of 300 mg RBP-6000.*

The PD measurement of interest was the E_{max} drug-liking assessment observed during each 3-day hydromorphone test session. The drug-liking is assessed using the unipolar Visual Analog Scale (VAS) in which a 10 cm strip of paper presented to a patient to whom points to the spot on the paper associated with their current amount of "like" for the drug. The 0 mm location represents minimal liking (neutral response) and the 100 mm location this represents the highest possible liking of the drug. The Applicant's analyses subtracted the drug-liking score for placebo (0 mg hydromorphone) from the drug-liking score for both the 6 mg and 18 mg hydromorphone doses

administered within each weekly 3-day testing session. The plot (Figure 10) below shows the distribution of placebo-corrected E_{max} drug-liking scores.

Figure 10 Distribution of Placebo-Corrected Drug-Liking Scores by Hydromorphone Dose Level and By Week



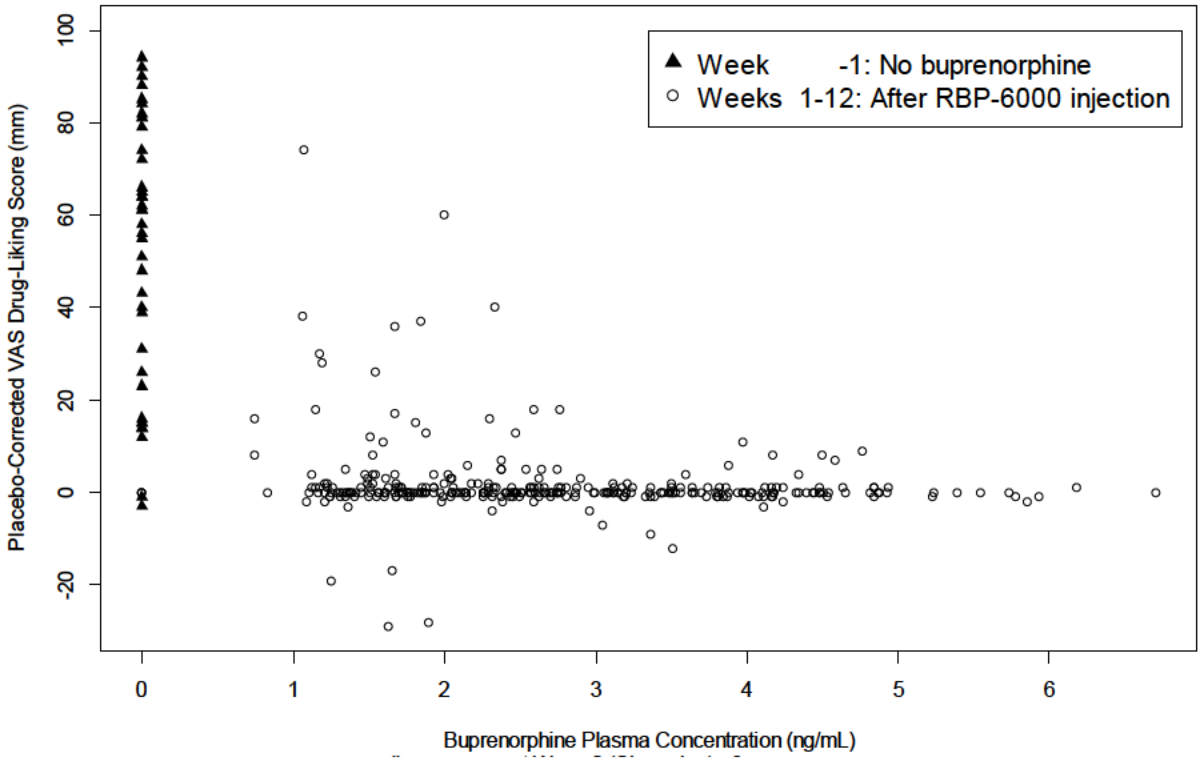
**Vertical yellow lines indicate the timing of SC injections of 300 mg RBP-6000. The red and blue boxplots represent the placebo-corrected E_{max} drug-liking score distribution observed during the hydromorphone challenge for 6 and 18 mg, respectively. The 6 mg and 18 mg hydromorphone sessions are presented in order of increasing hydromorphone dose level for ease of viewing but in the trial the hydromorphone dose sequence was randomized for each patient for each visit.*

Looking at the figure above, the following observations are apparent:

- drug liking is the highest during the qualification period, Week -1, where the hydromorphone challenge was conducted in the absence of buprenorphine;
- drug-liking is reduced after initiating RBP-6000 (at and after Week 1) compared to drug-liking assessed during baseline or qualification phase, as expected;
- RBP-6000 appears to be more effective at reducing the "drug liking" for the 6 mg hydromorphone dose level than for 18 mg, as expected;
- the drug-liking scores improve after the 2nd RBP-6000 administration (at and after week 5) compared to scores obtained after the 1st RBP-6000 administration. The improved scores after the 2nd administration are likely due to greater buprenorphine concentrations achieved during this period (which are approximately two times greater after the 2nd injection compared to the period after the first injection, Weeks 1 to 4, as shown in the previous slide).

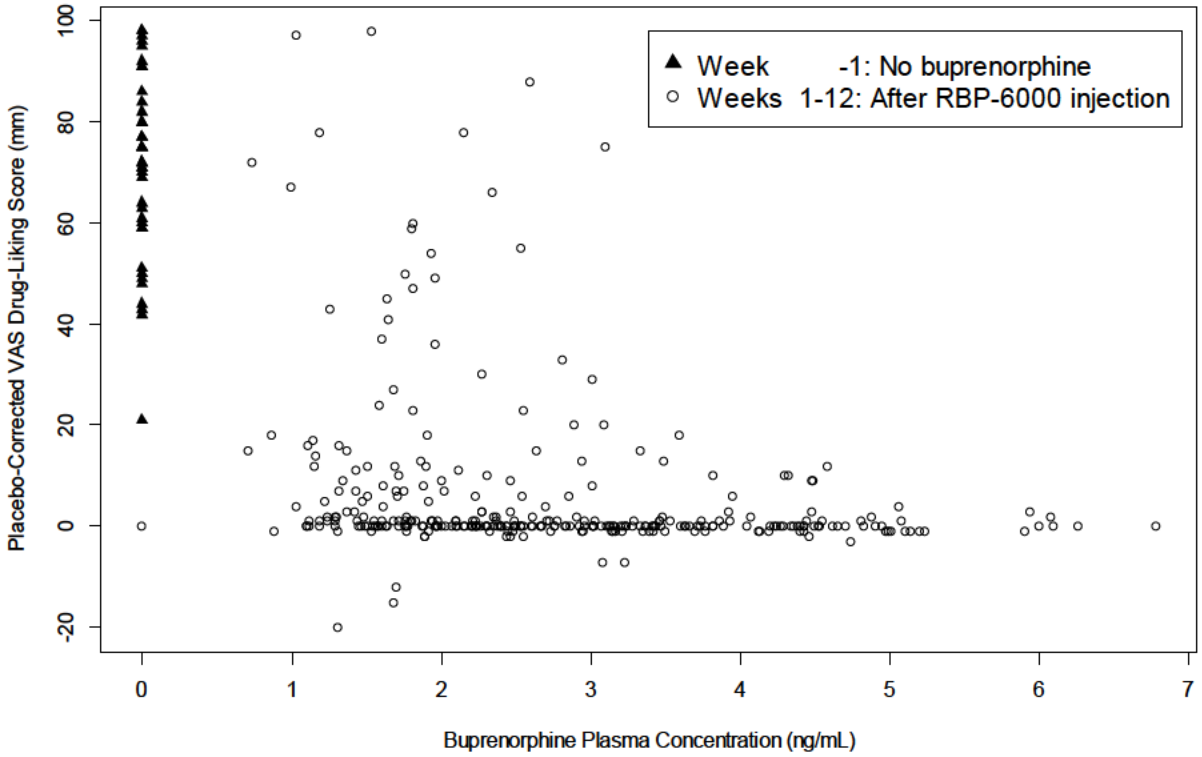
A graphical analysis was conducted to explore the relationship between PK and PD. Scatter plots were generated with PK data and the corresponding PD measurement for both the 6 mg hydromorphone dose (see Figure 11) and the 18 mg hydromorphone dose (see Figure 12).

Figure 11 Scatter Plot of Placebo-Corrected Drug-Liking Scores with Corresponding Buprenorphine Concentration for the 6 mg Hydromorphone Dose at Baseline and Throughout 12 Week Study Period



The solid triangle points represent the drug-liking scores observed during week -1 (baseline/qualification period) in the absence of buprenorphine and the circles represent observations acquired after initiating RBP-6000.

Figure 12 Scatter Plot of Placebo-Corrected Drug-Liking Scores with Corresponding Buprenorphine Concentration for the 18 mg Hydromorphone Dose at Baseline and Throughout 12 Week Study Period

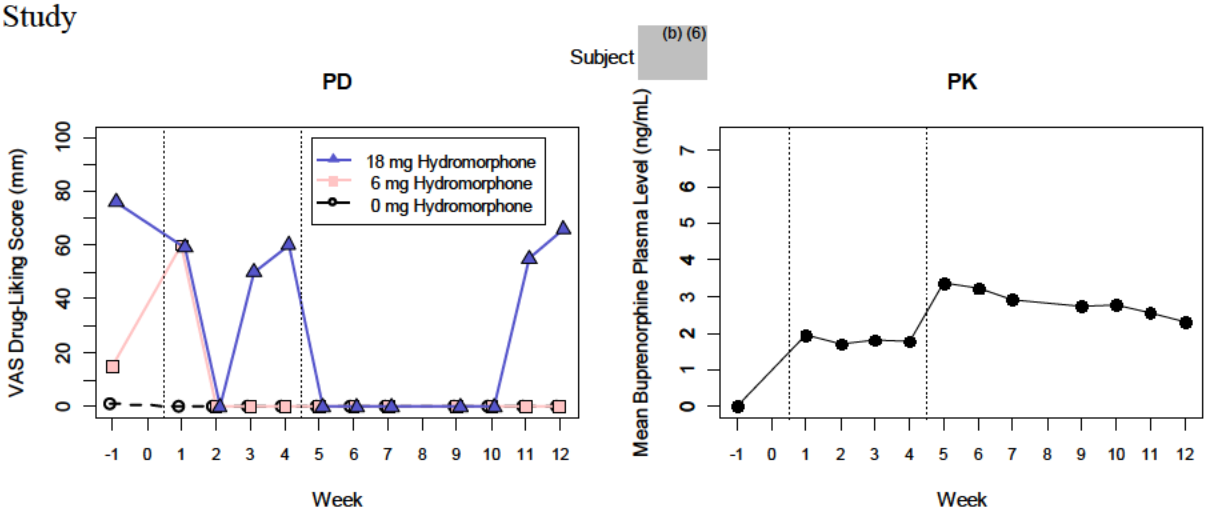


The solid triangle points represent the drug-liking scores observed during week -1 (baseline/qualification period) in the absence of buprenorphine and the circles represent observations acquired after initiating RBP-6000.

Overall, the data show an apparent central tendency of increasing effectiveness with increasing exposure. However, the scatter plots above also demonstrate that the dispersion in drug-liking scores is wider at the lower buprenorphine exposures compared to higher buprenorphine exposures. The dispersion in the drug-liking scores was further investigated to explore and potentially uncover a reason for the wide range of drug-liking scores observed at lower buprenorphine exposures.

When looking at the individual time course of buprenorphine concentration alongside the time course of drug-liking scores, several individuals appeared to present abrupt changes in the drug-liking scores from week to week. The following (Figure 13) plot shows the time-course of PK and PD data for one representative individual (subject (b) (6)), however, approximately one half of the subjects enrolled exhibited this phenomenon.

Figure 13 Representative Individual with Abrupt Changes in Drug-Liking Between Weeks of Study



The left panel shows abrupt changes in the drug-liking score from week-to-week (particularly from weeks 2-4 and weeks 11-12) for the 18 mg hydromorphone injection which do not appear to correlate with the PK profile. The reason for this phenomenon is currently unknown.

Overall, the available PK and PD data provide supportive evidence of opioid blockade. There is an overall trend of increasing response (that is, reduced drug-liking) with increasing buprenorphine exposure. As expected, higher buprenorphine exposures are required to reduce the drug-liking following an 18 mg hydromorphone challenge compared to a 6 mg hydromorphone challenge.

However, the data demonstrate that in some subjects the drug-liking score can undergo abrupt changes that do not appear to correlate with the PK profile. These observations, such as the PK and PD profiles for individual shown on the previous slide, suggest that, in addition to buprenorphine concentration, that other factors, factors which are currently unknown, are likely influencing the drug liking scores.

For additional details regarding these analyses, please refer to section 4.3.3 in the appendix.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

In patients with OUD who are utilizing SL products, the patients undergo stabilization and titration phases in order to get to the maintenance phase. The 24 mg SL dose is the maximum dose indicated in OUD patients. As previously discussed Sublocade clinical program was based on the development of an extended release formulation which delivers clinically relevant buprenorphine concentrations for at least 28 days without need for supplemental buprenorphine, e.g., "rescue" sublingual buprenorphine, while preventing any related safety concerns high buprenorphine concentrations for treatment of moderate to severe OUD in patients who have undergone

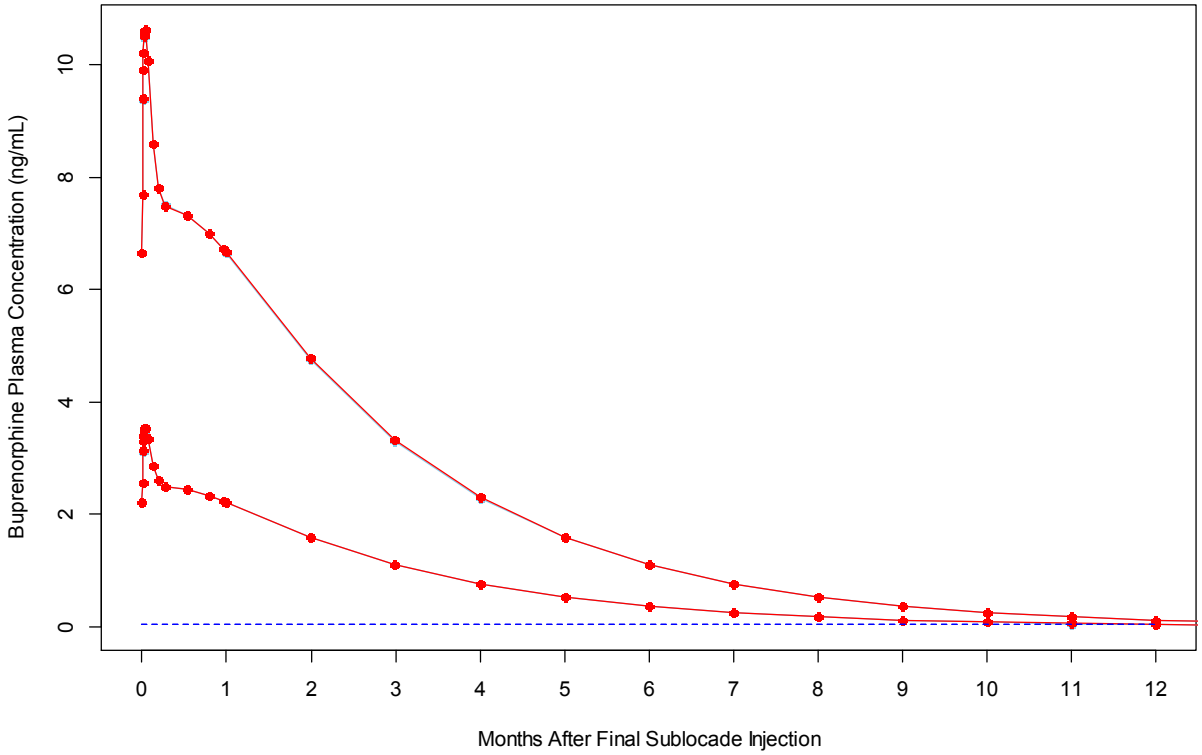
stabilization to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. In the blockade study 13-0002, two injections of 300 mg Sublocade demonstrated blockade of drug-liking for 6 mg hydromorphone as well as 18 mg hydromorphone. Additionally, in Trial 13-0001 where Sublocade 300 mg for 6 injections and Sublocade 300 mg for 2 injections followed by 100 mg for 4 injections, efficacywas demonstrated in treating patients with OUD. Therefore, it appears to be that the proposed dosing regimen appears to be appropriate for the patients with OUD who have undergone stabilization to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. See Section 3.3.3 for further information and discussion regarding the opioid blockade and efficacy studies.

3.3.2.1 How long does the drug remain in plasma after the final dose?

The time duration for which the drug remains in the plasma after the final dose of RBP-6000 is necessary to inform a label statement in section 2.4 regarding discontinuation of RBP-6000. The review team was interested to know how long after discontinuing RBP-6000 can patients be expected to test positive on a buprenorphine drug test. As such, OCPinvestigated the PK profile after the last injection of RBP-6000 at steady-state.

The reviewer conducted PK simulations to generate a PK profile following the final dose of RBP-6000 at steady-state for each proposed maintenance dose level (100 mg once monthly and 300 mg once monthly). The reviewer utilized the Applicant's population PK model to generate the PK simulations (please refer to section 4.3.1 and 4.3.2 in the appendix for details regarding the population PK model which OCP finds acceptable). The same initial dosing procedure as was used in the pivotal clinical trial 13-0001 and is proposed for labeling was utilized for PK simulations: 2 weeks of sublingual Subutex to stabilization at 10 mg once daily, two SC injections of 300 mg RBP-6000 separated by 1 month, followed by maintenance dosing of either 100 mg once monthly or 300 mg once monthly. After administering enough doses to represent long-term RBP-6000 use at steady-state (2 years of treatment), dosing was ceased and the PK profile was simulated for up to 1 year after the final dose (Figure 14) for both dose regimens.

Figure 14 Simulated PK Profile Following a Final Injection at Steady-State from a 300 mg Once Monthly Regimen and a 100 mg Once Monthly RBP-6000 Regimen



Time zero represents the final SC injection of RBP-6000 at steady-state from a 300 mg once monthly regimen (upper red series) and 100 mg once monthly regimen (lower red series). The blue dashed line represents the analytical assay LLOQ of 0.05 ng/mL.

Overall, for both maintenance dose levels of 100 and 300 mg once monthly, buprenorphine plasma concentration remains above the LLOQ of 0.05 ng/mL for the Applicant's assay for up to 12 months. In section 2.4 of the label a statement was inserted to indicate that the subjects discontinuing RBP-6000 may have detectable plasma levels of buprenorphine for up to 12 months. Please refer to section 4.2.4 in the appendix for additional details regarding PK simulations for assessing the PK profile after the final injection.

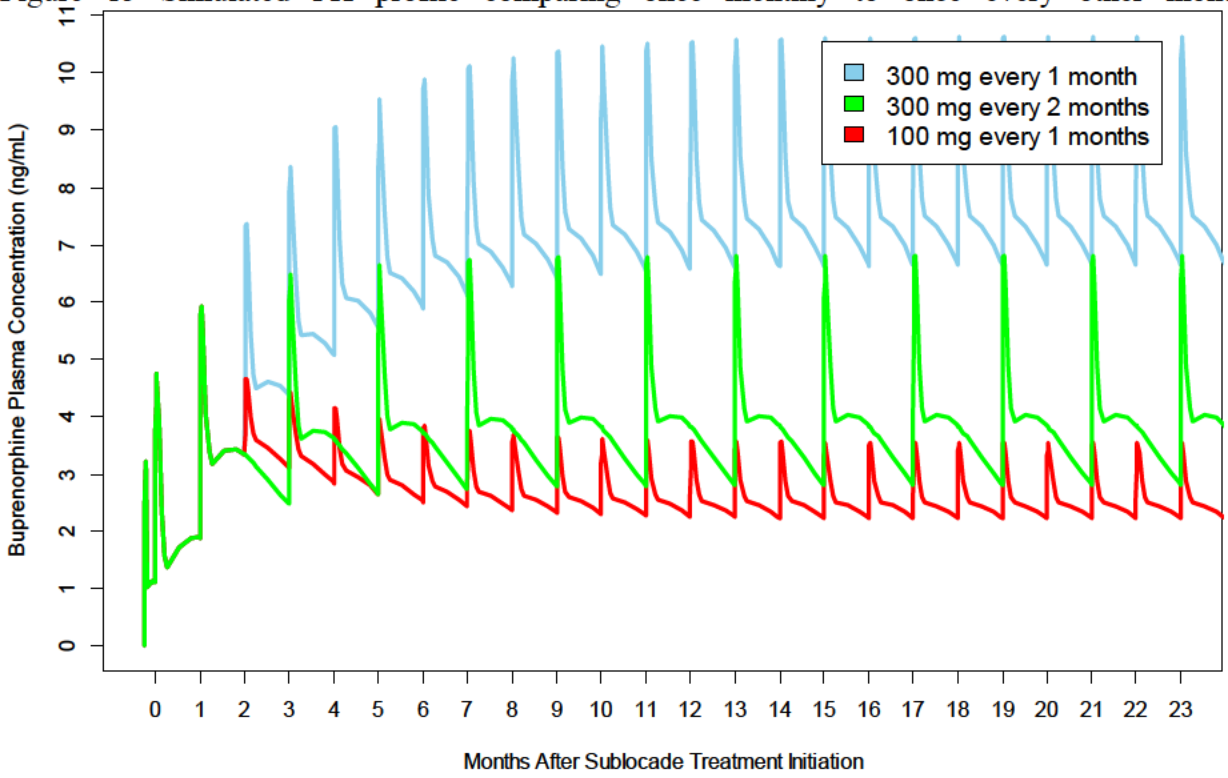
3.3.2.2 What is the effect of increasing dosing interval on PK?

Based on the relatively flat PK profile observed after administration of RBP-6000 and due to concerns about safety at the 300 mg dose, OCP assessed the possibility of a longer dosing interval on RBP-6000 exposure.

The reviewer conducted PK simulations to generate a PK profile following the final dose of RBP-6000 at steady-state for each proposed maintenance dose level (100 mg once monthly and 300 mg once monthly). The Applicant's population PK model was utilized to generate the PK simulations (please refer to section 4.2.1 and 4.2.2 in the appendix for details regarding the population PK model which OCP finds acceptable). The same initial dosing procedure as was used in the pivotal clinical trial 13-0001 and is proposed for labeling was utilized for PK simulations; 2 weeks of

sublingual Subutex to stabilization at 10 mg once daily, two SC injections of 300 mg RBP-6000 separated by 1 month, followed by maintenance dosing. In addition to the maintenance dose regimens that were studied in the pivotal trial 13-0001 and proposed labeling (100 mg once monthly and 300 mg once monthly) a maintenance regimen of 300 mg once every 2 months was assessed. The following plot (Figure 15) shows the comparison of the simulated PK profile for maintenance regimens of 300 mg once monthly, 300 mg once every other month, and 100 mg once monthly.

Figure 15 Simulated PK profile comparing once monthly to once every other month



The blue, green, and red series represent maintenance doses of 300 mg mg every month, 300 mg every other month, and 100 mg every month. From -0.5 months until 2 months, all 3 series receive the same regimen: 2 weeks of SL Subutex 10 mg, 300 mg SC RBP-6000 at Month 0, 300 mg SC RBP-6000 at Month 1. Thus, all 3 series are identical from Month 0 to Month 2 (and only the green series is displayed from Month 0 to Month 2).

Overall, the PK simulations suggest that exposures for a maintenance dose of 300 mg once every other month are likely to be within the exposures achieved with maintenance doses of 100 mg once monthly and 300 mg once monthly. As both the 100 and 300 mg once monthly maintenance dose levels demonstrated efficacy in the pivotal trial, this finding suggests that 300 mg once every other month may be an efficacious dose regimen which could reduce the number of injections by 50% (6 instead of 12 injections per year). Based on discussions with Clinical team, these findings suggest that longer dosing intervals should be explored.
Please refer to section 4.2.5 in the appendix for additional details regarding PK simulations for assessing the PK profile after the final injection.

3.3.3 What are the characteristics of the dose-systemic exposure relationships for efficacy?

The review of efficacy of RB-6000 focused on the findings from two trials: an inpatient opioid blockade study (RB-US-13-0002) followed by a randomized, double-blind, placebo-control efficacy study (RB-US-13-0001). In opioid blockade study the relationship of buprenorphine concentrations with mu-opioid receptor occupancy, opioid withdrawal symptoms, and opioid agonist effects were assessed. In efficacy study, two dosing regimens were assessed against placebo treatments.

Exposure-Response Analyses of Mu-opioid Receptor Occupancy

The Applicant conducted analyses to assess the relationship of buprenorphine concentrations with mu-opioid receptor occupancy, opioid withdrawal symptoms, and opioid agonist effects. Data were pooled from two published studies in which heroin-dependent patients received sublingual (SL) buprenorphine.

Study 1 (Greenwald 2003[1]): Five heroin-dependent subjects received SL buprenorphine escalation from 4-16 mg/day through Days 1-7 then 32 mg/day for 12 days. On Day 8 a 24 mg IM hydromorphone challenge dose was administered and subjective withdrawal symptoms were assessed. Buprenorphine and norbuprenorphine PK samples were assessed on Day 9. Opioid withdrawal symptoms were assessed on Days 10 and 11 before and 1, 2, 3, 6, and 12 hours after SL buprenorphine administration. On Day 12 a PET scan with [^{11}C]-carfentanil was administered 4 hours after SL buprenorphine to assess mu-opioid receptor occupancy in the brain. Subjects were down-titrated from 16 mg/day for 12 days, 2 mg/day for 14 days, 0 mg/day for 12 days with PET scans, hydromorphone challenge, and withdrawal symptoms assessed at each dose level.

Study 2 (Greenwald 2007[2]): Ten heroin-dependent subjects received buprenorphine SL tablets 16 mg/day for ≥ 2 weeks. Buprenorphine plasma PK samples, opioid withdrawal symptoms, and 4 hydromorphone challenges (24 mg IM) or 4 PET brain scans with [^{11}C]-carfentanil were conducted at 4, 28, 52, and 76 hours after the final buprenorphine dose.
Both studies utilized an opioid symptom questionnaire with 16 agonist effect questions and 16 withdrawal scale questions. Each question can have a score of 0 ("not at all") to 4 ("extremely"). Thus, each set of 16 questions can yield a range of 0 to 64. Buprenorphine attenuation (blockade) of hydromorphone agonist effects was measured by VAS including "Any drug effect", "High", "Good Drug Effect", "Bad Drug Effect", "Stimulated", "Sedated", "Liking" or "Anxious." From both trials, whole-brain imaging results were used to calculate mu-opioid receptor availability.

[1] Greenwald MK, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta JK. Effects of Buprenorphine Maintenance Dose on [mu]-Opioid Receptor Availability, Plasma Concentrations, and Antagonist Blockade in Heroin-Dependent Volunteers. Neuropsychopharmacology. 2003 Nov 1;28(11):2000.
[2] Greenwald M, Johanson CE, Bueller J, Chang Y, Moody DE, Kilbourn M, Koeppe R, Zubieta JK. Buprenorphine duration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. Biological psychiatry. 2007 Jan 1;61(1):101-10

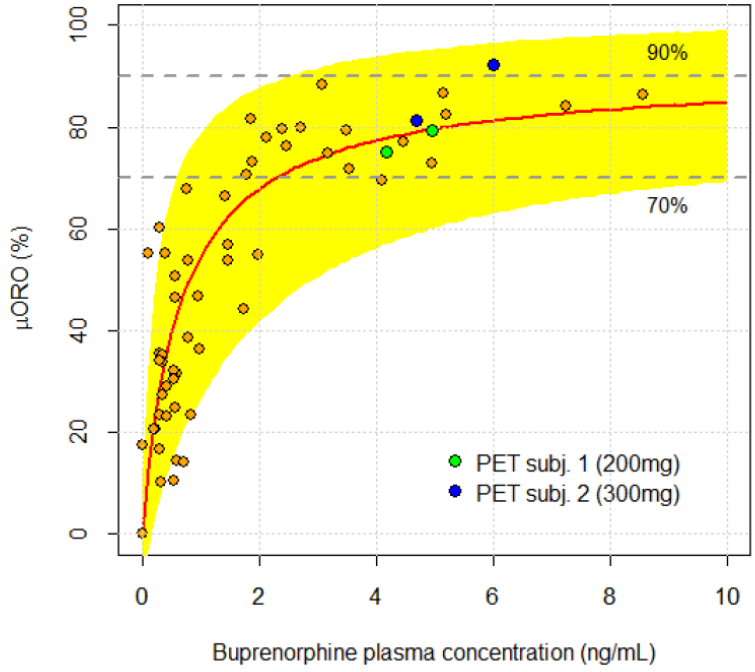
The percentage of mu-opioid receptor occupancy was calculated as 100 minus mu-opioid receptor availability.

The Applicant pooled the data from Studies 1 and 2 (total of 59 PK/mu-opioid receptor occupancy measurements) and utilized an Emax model to fit the data. This approach requires an assumption of a direct exposure-occupancy relationship with negligible equilibration delay and negligible contribution of norbuprenorphine.

$$\mu ORO = \frac{E_{max} \times C_p}{EC_{50} + C_p}$$

The muORO term is mu-opioid receptor occupancy, C_p is the buprenorphine plasma concentration, and EC_{50} is the buprenorphine plasma concentration achieving 50% of the maximal mu-opioid receptor occupancy (E_{max}). The Applicant provided the following graphical comparison (Figure 16) of observations with simulated predictions.

Figure 16 Visual predictive check for the PK/PD model relating whole-brain mu-opioid receptor occupancy to buprenorphine plasma concentration



µORO=mu-opioid receptor occupancy
Red line=median model prediction; Shaded yellow area=5th and the 95th percentiles of the simulated data;
Orange dots=individual measurements used to build the model
The green and blue dots are the observed data points obtained for the subjects receiving either 200 mg or 300 mg of RBP-6000 in the PET scan sub-study of the MAD study (Study 12-0005).
Source: adapted from INDV-6000-M02 Figure 3

(*source: summary-clin-pharm.pdf, page 67 of 148*)

The final model estimates were an Emax of 91.4% mu-opioid receptor occupancy (residual squared error [RSE] 4.3%) and EC_{50} of 0.67 ng/mL (28% RSE). The model-predicted variability (shaded yellow area) appears to be overestimated at higher concentrations (e.g. > 3 ng/mL).

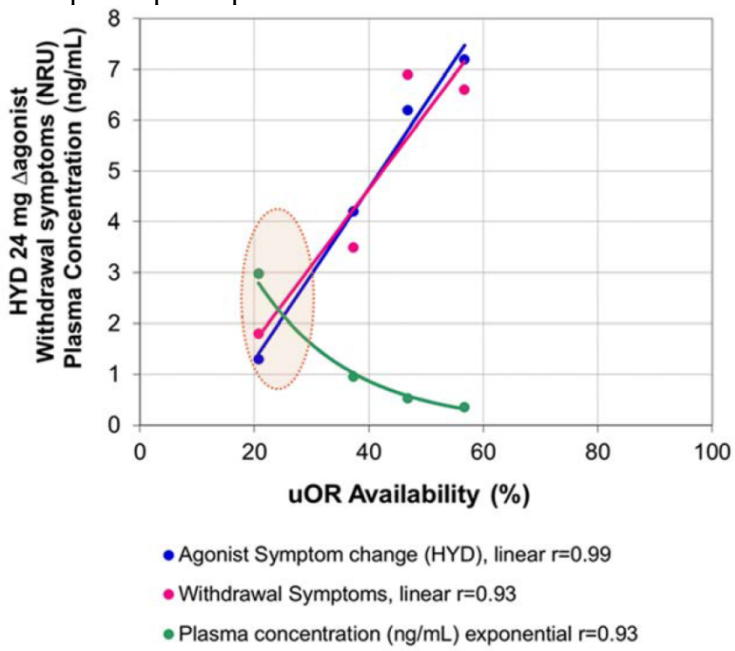
As a cross-study comparison, the Applicant superimposed the PK and mu-opioid receptor occupancy data from two subjects who underwent a PET scan sub-study in their Phase 2 multiple ascending dose Study RB-US-12-0005. For the subject receiving 200 mg in the MAD study, brain mu-opioid receptor occupancy was 79% on the 7th day and 75% on the 28th day post-dose. For the subject receiving 300 mg, brain mu-opioid receptor occupancy was 92% on the 7th day and 81% on the 28th day post-dose. These data collected from Study RB-US-12-0005 are consistent with the model predictions based on literature data from the two Greenwald studies.

Exposure-Response Analyses of Attenuation (i.e., Blockade) of Hydromorphone Agonist Effects

The Applicant assessed the relationship of mu-opioid receptor availability with withdrawal symptom scores (red points in figure below) and hydromorphone-induced changes in agonist symptoms (blue points in figure below) using data from Greenwald Study 1 and Greenwald Study 2. The Applicant utilized a linear model to assess the relationship between mu-opioid receptor availability and these two measures (red line and blue line in Figure 17 below). The Applicant

plotted the buprenorphine plasma concentration profile associated with various levels of mu-opioid receptor availability (green dots in plot below) and used a nonlinear model to describe the relationship between plasma concentration and mu-opioid receptor availability (green line in figure below). The Applicant states that mu-opioid receptor occupancy of ≥ 70% corresponds to mu-opioid receptor availability of ≤ 30% (tan shaded oval in figure below, Figure 17).

Figure 17 Observed and model predicted changes in agonist effect following administration of 24 mg hydromorphone, observed and model predicted mean withdrawal symptoms, and observed and model predicted buprenorphine plasma concentration in relation to mu-opioid receptor availability

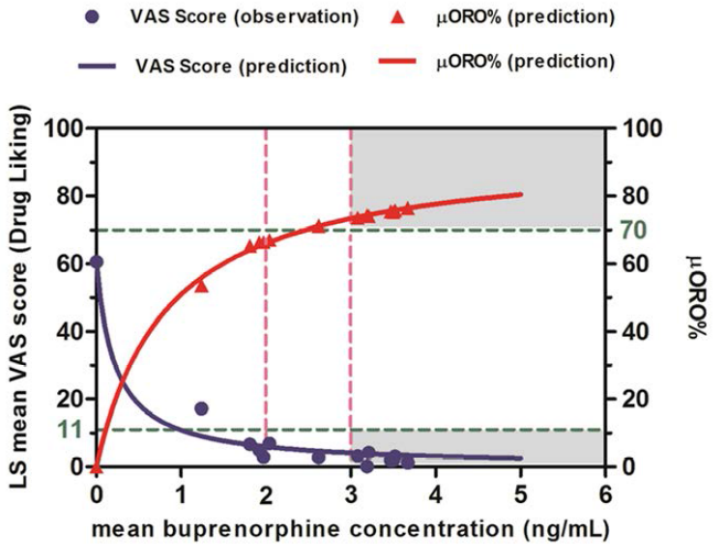


Dots=mean observations; Solid lines=model predictions by linear or nonlinear regression analysis
HYD=hydromorphone
Souce: individual data from 2 previously published clinical trials (Greenwald 2003; Greenwald 2007)
(*source: summary-clin-pharm.pdf, page 68 of 148*)

Exposure-Response Analyses of "Drug-Liking" Scores

In Study RB-US-13-0002, the Applicant applied the "Drug Liking" Visual Analogue Scale (VAS) survey to assess the ability of 2 SC injections of 300 mg RBP-6000 every 28 days to block the subjective effects of hydromorphone (6 mg or 18 mg IM hydromorphone). The Applicant utilized the PK / mu-opioid receptor occupancy model to predict brain mu-opioid receptor occupancy as a function of plasma buprenorphine concentration (red points, red line in Figure 18). The plot also includes the observed VAS scores with the associated observed plasma buprenorphine concentration (black dots in figure below). The model predicted relationship between VAS score and buprenorphine exposure obtained using a maximal inhibitor (Imax) model is displayed as the black curve in figure below (Figure 18).

Figure 18 Observed differences in drug liking from placebo and mean predicted mu-opioid receptor occupancy as a function of buprenorphine plasma concentration after the 18 mg hydromorphone challenge



µORO=mu-opioid receptor occupancy; LS=least squares
Red triangles=mean of µORO individual predictions; Red curve=mean model predictions; Blue dots=mean VAS scores; Blue curve=model predictions after fitting with a maximal inhibitory (Imax) model
Source: CSR 13-0002 Figure 40
(*source: summary-clin-pharm.pdf, page 70 of 148*)

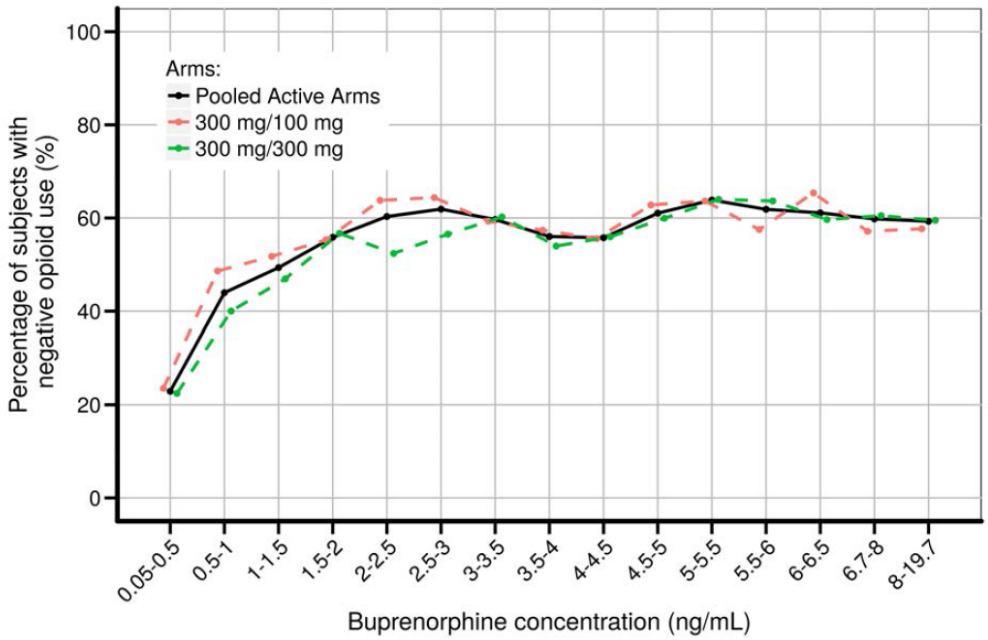
Applicant concludes that mean buprenorphine plasma concentrations ≥ 2 ng/mL were associated with mean drug-liking VAS score below 11 (Applicant's non-inferiority boundary; lower black dashed line in figure above). Applicant states that brain mu-opioid receptor occupancy levels were ≥ 70% for buprenorphine concentration ≥ 3 ng/mL and ≥ 60% for buprenorphine concentrations ≥ 2 ng/mL.

[*Reviewer comment: The Applicant's analyses based on mean drug-liking scores were not acceptable to the Division. The maximum drug-liking response within a 300-minute testing session is the appropriate metric. Please refer to section 4.3.3 for details.*]

Graphical Analyses of Relationship Between Clinical Endpoints and Buprenorphine Exposure

The Applicant assembled plots to display the relationship between negative opioid use (based on patient self-reporting of opioid use) and buprenorphine plasma concentration in Study 13-0001. The observed data regarding proportion of patients with negative opioid use appears to plateau near 60% (see, **Error! Reference source not found.**19).

Figure 19 Relationship between the proportion of subjects with negative opioid use and buprenorphine plasma concentration (Study RB-US-13-0001)



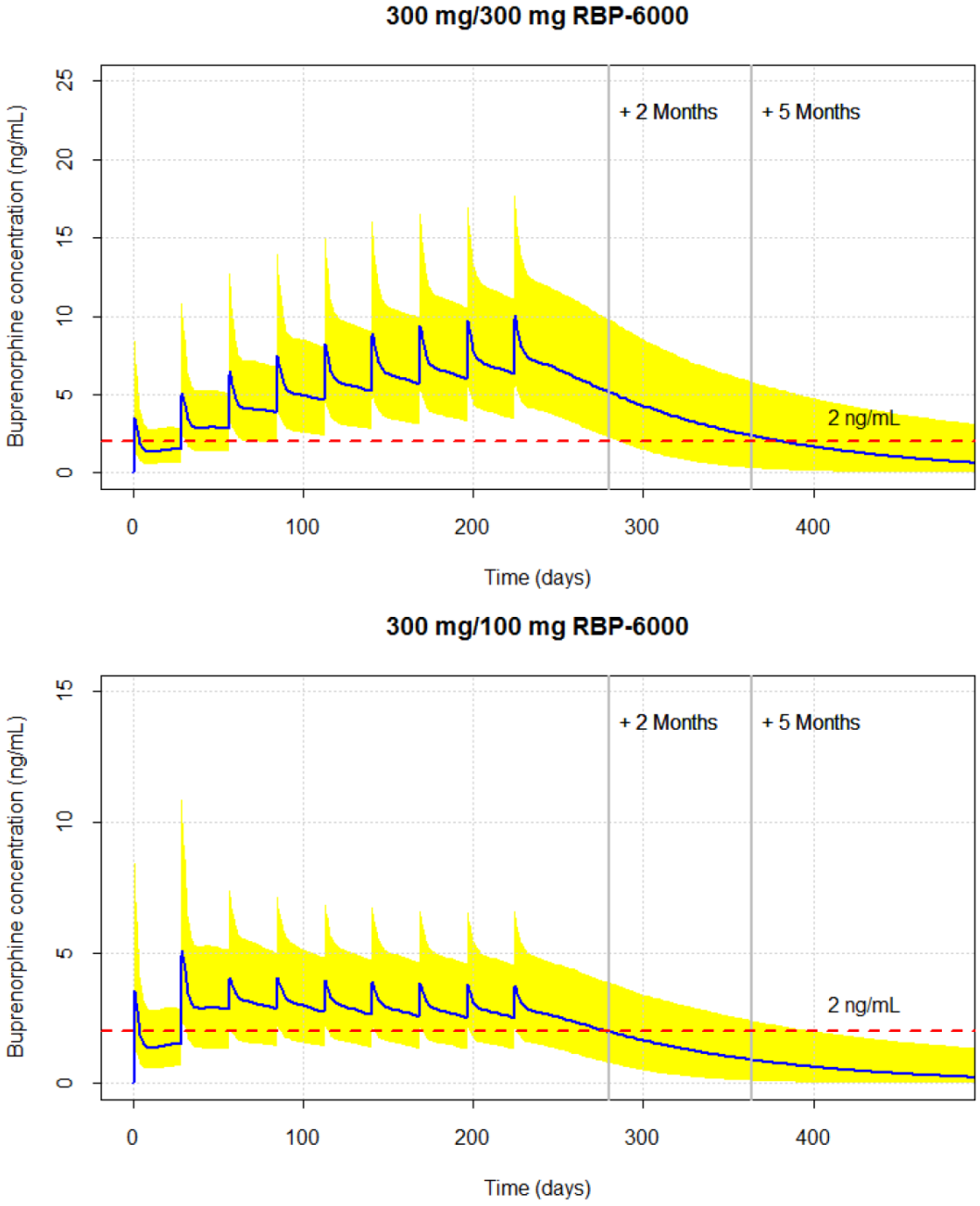
Curves=percentage of subjects with negative opioid use in the 300 mg/100 mg arm (red curve), 300 mg/300 mg arm (green curve) and for the 2 arms pooled (black curve)
Source: INDV-6000-M04 Figure 9

(*source: summary-clin-pharm.pdf, page 76 of 148*)

Exposure-response analyses for negative opioid use were conducted using an Emax model. The results indicate that subjects who used illicit opioids via the injectable route had a 3.6 times greater EC_{50} (4.3 ng/mL) than the EC_{50} for subjects who used illicit opioids via other routes (1.2 ng/mL). This suggests that patients who use illicit opioids via the injectable route require greater buprenorphine exposure to avoid illicit opioid use than patients who use illicit opioids by other routes.

Pharmacokinetic simulations were conducted to facilitate comparison of the exposures associated with the proposed doses in the context of the 2 ng/mL exposure level (Figure 20).

Figure 20 Predicted decrease in buprenorphine plasma concentrations for the 300 mg/300 mg and 300 mg/100 mg dosing regimens of rbp-6000 after the last sc injection



Blue curve=medians of the simulated data; Shaded yellow area=90% prediction intervals of simulated data
A total of 9 SC injections were simulated. The horizontal red dashed line indicates the 2 ng/mL minimum concentration required for opioid blockade, as established from modelling and simulation and confirmed by the findings of the opioid blockade study (13-0002) (see Section 2.7.2.3.3.1 for details).
Model used for simulation: INDV-6000-M04 Table 12

Overall, there is a consistent trend among the measures assessed in exposure-response analyses. Overall, for mu-receptor occupancy, change in mean VAS (Drug Liking) score and percentage of subjects with negative opioid use, there is an apparent increase in response with increasing

exposure. Applicant concludes that there is an apparent "plateau" of where the PD responses are at their maximum at a buprenorphine concentration range above 2-3 ng/mL.

According to the Applicant, their PK simulations of the proposed dosing regimens (300 mg / 100 mg) and (300 mg / 300 mg) appear to be able to, on average, achieve exposures throughout the dosing interval that are associated with the maximum effect PD.

[*Reviewer comment: The aforementioned PD measures (% μORO, withdrawal symptoms, agonist symptoms, drug liking, and proportion of patients with negative opioid use) appear to plateau at higher end of buprenorphine exposure range. However, many of these analyses are based on mean PD responses within the population and do not account for PD variability. One measure for which variability is quantified is for μORO shown in Figure 16. In Figure 16, at a buprenorphine concentration of 2 ng/mL, approximately half of the patient can be expected to have μORO in the range of 40% to 70%. Overall, the available data suggest that a subset of patients may not obtain adequate benefit from buprenorphine exposure in the range of 2-3 ng/mL. Based on the available data, the value of a minimum therapeutic concentration is not apparent. This observation lends support to the dosing plan to start maintenance dosing at 100 mg once monthly and to only increase to 300 mg once monthly if clinically necessary.*]

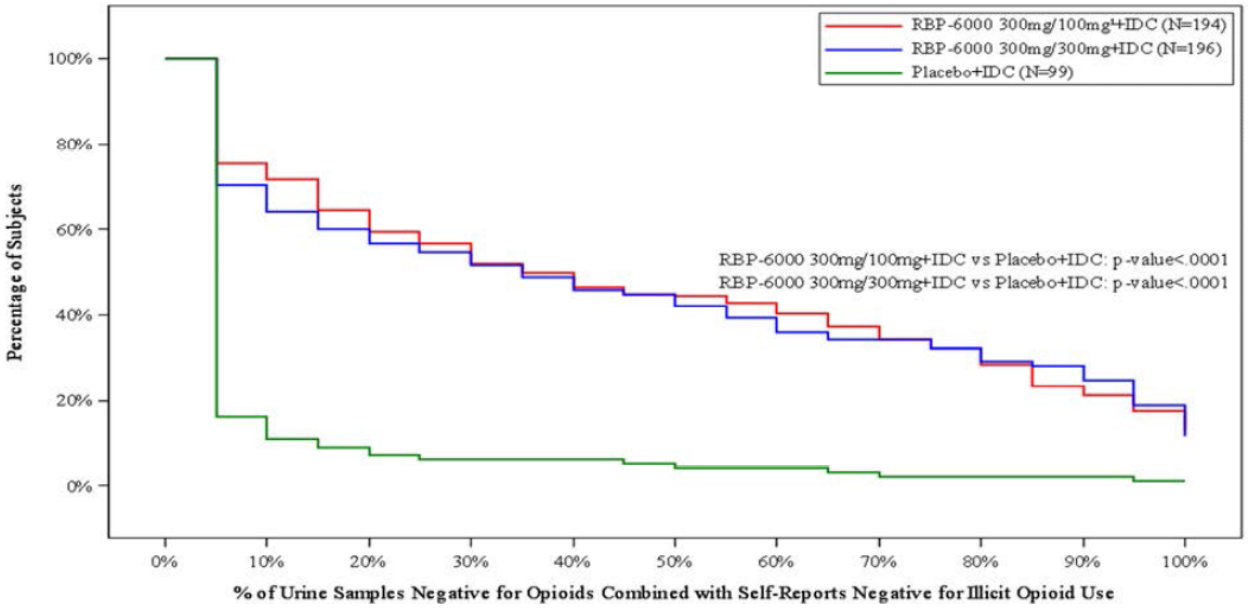
RB-US-13-0001: Efficacy study (The reader is referred to Clinical Review by Drs. Emily Deng and Feng Li, OND and OTS/OB, respectively)

Study RB-US-13-0001 was a Phase 3, randomized, double-blind, placebo-controlled, multi-center study which assessed the efficacy, safety and tolerability of multiple Sublocade injections over 24 weeks [Treatment 1: Sublocade 300 mg for 6 injections (once every 28 days); Treatment 2: Sublocade 300 mg for 2 injections (followed by 100 mg for 4 injections (once every 28 days)] in treatment-seeking subjects with a diagnosis of moderate or severe OUD. Subjects were inducted onto Suboxone SL film for 3 days, followed by a Suboxone SL film run-in dose-adjustment period (4- to 11-day) to achieve buprenorphine doses ranging from 8 to 24 mg/day. For placebo treatments, patients were administered a placebo injection that was volume-matched for Sublocade 300 mg or 100 mg injections.

The primary efficacy was assessed by centrally tested urine drug screen (UDS) results (urine samples negative for opioids) and self-reported illicit opioid (percentage abstinence) use as recorded by the patient from Week 5 through Week 24. Additionally, scores for Opioid Craving VAS, Clinical Global Impression-Severity (CGI-S) scale, Clinical Global Impression-Improvement (CGI-I) scale, COWS and SOWS were assessed. Urine drug screens and self-reports were assessed at screening, and on a weekly basis following each Sublocade SC injections or placebo (Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, 106, 113, 120, 127, 134, 141, 148, 155, 162 and 169), as well as at a safety follow-up visit (Day 197). Urine drug screens were also assessed on the day after each SC injection at 24 h post-dose (Days 2, 30, 58, 86, 114 and 142). The Applicant presented the following results.

The Figure 21 shows the Cumulative Distribution Function (CDF) of percent abstinence from Week 5 through Week 24. Table 22 shows the same information in a tabulated format.

Figure 21 Primary Efficacy Endpoint: Cumulative Distribution Function of the Percentage Abstinence from Week 5 Through Week 24-Full Analysis Set (Study 13-0001)



IDC = individual drug counselling
Note: Subjects from Site 20 were excluded from the analysis. All missing results for opioids were considered non-negative. Depicted data are inverse-cumulative distribution function.
1 Subjects received RBP-6000 containing 300 mg buprenorphine for the first 2 injections, followed by 4 injections of RBP-6000 containing 100 mg buprenorphine. Note the other active treatment group received 300 mg buprenorphine for all 6 injections.
Source: CSR 13-0001 Figure 14.2.1.1.1

Table 22Primary efficacy endpoint: cumulative distribution function of the percentage abstinence from Week 5 Through Week 24-Full Analysis Set (Study 13-0001)

	Number (%) of Subjects		
Percentage Abstinence	RBP-6000 300mg/100mg+IDC (N=194)	RBP-6000 300mg/300mg+IDC (N=196)	Placebo+IDC (N=99)
≥ 0%	194 (100.0)	196 (100.0)	99 (100.0)
≥ 10%	139 (71.6)	126 (64.3)	11 (11.1)
≥ 20%	115 (59.3)	111 (56.6)	7 (7.1)
≥ 30%	101 (52.1)	101 (51.5)	6 (6.1)
≥ 40%	90 (46.4)	90 (45.9)	6 (6.1)
≥ 50%	86 (44.3)	82 (41.8)	4 (4.0)
≥ 60%	78 (40.2)	70 (35.7)	4 (4.0)
≥ 70%	66 (34.0)	67 (34.2)	2 (2.0)
≥ 80%	55 (28.4)	57 (29.1)	2 (2.0)
≥ 90%	41 (21.1)	48 (24.5)	2 (2.0)

IDC = individual drug counselling; Max = maximum; Min = minimum; SD = standard deviation
Note: The primary endpoint, percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use, is "percentage abstinence." Subjects from Site 20 were excluded from the analysis.

All missing results for opioids were considered non-negative.
a Wilcoxon rank-sum test was used to compare the treatment groups. Each dosing regimen was compared to placebo with respect to the composite primary efficacy endpoint at a significance level of α=0.025.
Source: CSR 13-0001 Table 14.2.1.1

Both the Sublocade 300 mg/300 mg and 300 mg/100 mg groups were statistically different from placebo ($P < 0.0001$ for both groups) in percentage abstinence from Week 5 through Week 24, indicating that Sublocade is efficacious in both treatment arms for treating patients with OUD.

As a secondary endpoint, the Table 23 shows Cumulative Distribution Function of the percentage of urine samples negative for opioids From Week 5 Through Week 24.

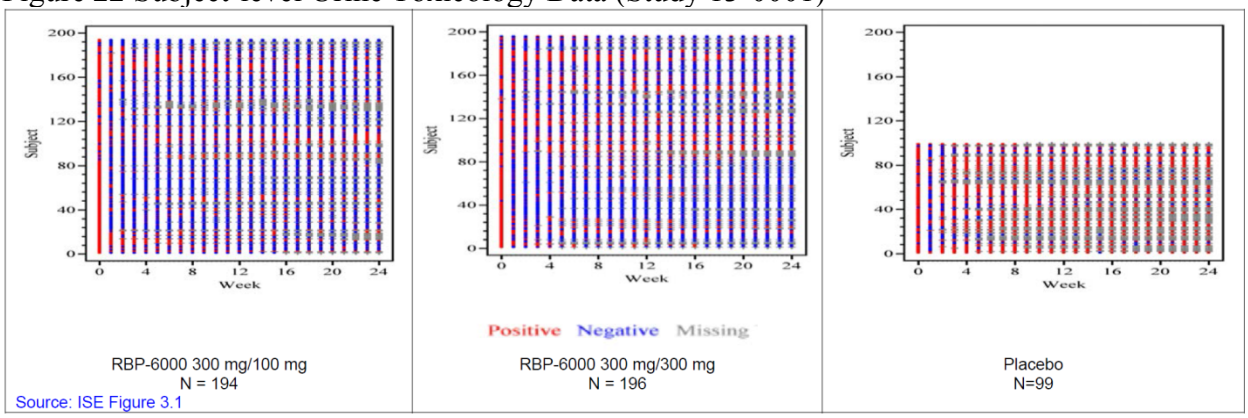
Table 23 Cumulative Distribution Function of the percentage of urine samples negative for opioids From Week 5 Through Week 24 - Full Analysis Set (Study 13-0001)

	Number (%) of Subjects		
Percentage Abstinence	RBP-6000 300mg/100mg+IDC (N=194)	RBP-6000 300mg/300mg+IDC (N=196)	Placebo+IDC (N=99)
□□0%	194 (100.0)	196 (100.0)	99 (100.0)
□□10%	140 (72.2)	129 (65.8)	17 (17.2)
□□20%	120 (61.9)	114 (58.2)	9 (9.1)
□□30%	106 (54.6)	109 (55.6)	8 (8.1)
□□40%	97 (50.0)	98 (50.0)	7 (7.1)
□□50%	91 (46.9)	88 (44.9)	6 (6.1)
□□60%	82 (42.3)	74 (37.8)	5 (5.1)
□□70%	73 (37.6)	69 (35.2)	4 (4.0)
□□80%	64 (33.0)	61 (31.1)	4 (4.0)
□□90%	47 (24.2)	51 (26.0)	2 (2.0)

IDC = individual drug counselling; Max = maximum; Min = minimum; SD = standard deviation
Note: Subjects from Site 20 were excluded from the analysis. All missing results for opioids were considered non-negative for opioids.
Source: CSR 13-0001 Table 14.2.3.1.1

The Figure 22 shows the subject-level urine toxicology data, which each individual subject is represented along the y-axis and study weeks are presented on the x-axis. Red symbols represent opioid-positive urine samples, blue symbols represent opioid-negative urine samples, and, grey symbols represent missing urine data.

Figure 22 Subject-level Urine Toxicology Data (Study 13-0001)



In both Sublocade treatment groups, the percentages of subjects achieving treatment success were considerably greater than for placebo as evidenced by more opioid-negative (blue) data points while the placebo group has more opioid-positive (red) or missing (grey) data points, indicating that Sublocade is efficacious in both treatment arms for treating patients with OUD.

3.3.4 What are the characteristics of the dose-systemic exposure relationships for safety?

No formal PK/PD studies were conducted in this NDA to establish the relationship between exposure and safety.

3.3.5 Does this Drug Prolong the QT or QTc Interval?

No formal QTc study was conducted in this NDA to establish the effect on QT. However, the exposure (concentration)-response relationship for QT was assessed (nonlinear mixed effects modelling (NONMEM)) by the Applicant using data from 5 clinical studies, including the Phase 3 efficacy study (Study 13-0001). For a complete review of QT analysis, the reader is referred to Dr. Gopichand Gottipati's review. A cursory overview of the QT information provided by the Applicant is presented below.

Time-matching buprenorphine concentrations and 12-lead ECGs were pooled across clinical studies. The QTc population was defined as all subjects who had a least 1 paired concentration and QT measurement at baseline/screening and following treatment with SL buprenorphine, RBP-6000 or placebo. The Applicant stated that the full dataset included 11925 observations from 1114 OUD subjects from the following 5 clinical studies:

- Study 10-0011: a single injection of 20 mg RBP-6000; matched concentrations and single 12-lead ECG measurements (110 samples) from 12 subjects;
- Study 11-0020: a single injection of 50 mg, 100 mg or 200 mg RBP-6000 (Cohorts 1-3), or a single SC injection of 100 mg RBP-6000 following 7 consecutive days on SUBOXONE SL tablets to achieve a stable buprenorphine dose of 12 mg/day (Cohort 4);

matched concentrations and single 12-lead ECG measurements (767 samples) from 48 subjects;

- Study 12-0005: multiple RBP-6000 300 mg doses and Subutex tablets (lead-in stable doses) ranged between 8 and 24 mg/day; matched concentrations and single 12-lead ECG measurements (1241 samples) from 122 subjects, where 87 subjects received repeated (≥ 4) SC injections of RBP-6000 following induction and stabilization on Subutex, and 35 subjects on Subutex tablets alone;
- Study 13-0006: a single injection of 300 mg RBP-6000 with either low, intermediate or high MW of ATRIGEL polymer, following induction and dose stabilization with SUBOXONE SL film to achieve a stable buprenorphine dose of 12 mg/day; matched concentrations and single 12-lead ECG measurements (543 samples) from 66 subjects, where 46 subjects received RBP-6000 and 20 subjects received Suboxone film alone;
- Study 13-0001: RBP-6000 300 mg/300 mg or 300 mg/100 mg doses; Suboxone film dose doses ranged from 8 to 24 mg/day; matched concentrations and single or triplicate 12-lead ECG measurements collected with and without Holter monitoring (9264 samples) from 866 subjects, where 437 subjects have matched screening records but were not randomized and 429 subjects were randomized to receive the placebo or RBP-6000 (300 mg/300 mg or 300 mg/100 mg).

Many of the concomitant medications or illicit drugs taken by OUD patients have the potential to affect QT and/or heart rate (HR). Thus, the Applicant stated that the concomitant or illicit drug effects on HR and/or QT interval were considered for in the modelling prior to establishing a baseline QTc and determining whether there was a drug related effect of buprenorphine on QT.

The Applicant stated that a concentration-QT model was developed to estimate the QTc in the absence of buprenorphine (QTcAbs), to estimate the parameter describing the QT-RR interval relationship (α), to estimate concomitant medication effects on α or QTcAbs, and to estimate a buprenorphine or norbuprenorphine-related slope (describing drug-related effects on QTc). The concentration-related effects of RBP-6000 on QT (which is a combination of different α values depending on whether subjects are on or off certain concomitant medications plus any RR interval effects due to buprenorphine) were tested using a linear concentration-related slope.

The covariates evaluated on α include withdrawal signs and symptoms (Clinical Opiate Withdrawal Scale-COWS), drugs used to treat withdrawal symptoms (i.e., clonidine, methocarbamol), illicit drugs (cocaine, phencyclidine, cannabinoids, barbiturates, and methamphetamines), drugs that may be used illicitly or licitly (e.g., amphetamines), and other drugs known to affect HR where there was sufficient data available from at least 25 subjects (e.g., albuterol). The covariates evaluated on QTcAbs include sex, age, opioids (i.e., methadone, oxycodone, hydrocodone, morphine, hydromorphone, oxymorphone, heroin, codeine), benzodiazepines, barbiturates, triplicate vs single ECG readings, central vs non-centrally read ECGs and Holter vs non-Holter. The Applicant stated that a Fredericia correction was selected for the analysis, because other corrections (including individual correction) did not improve the fit. The Applicant reported that the results indicate a non-positive slope of -0.0507 msec per ng/mL of buprenorphine; the slope indicated no potential of RBP-6000 to prolong the QTc interval. The relationship with norbuprenorphine also showed a non-positive slope. The Applicant further reported that the changes in QTc (largest to smallest) were associated with age (+16.8-msec

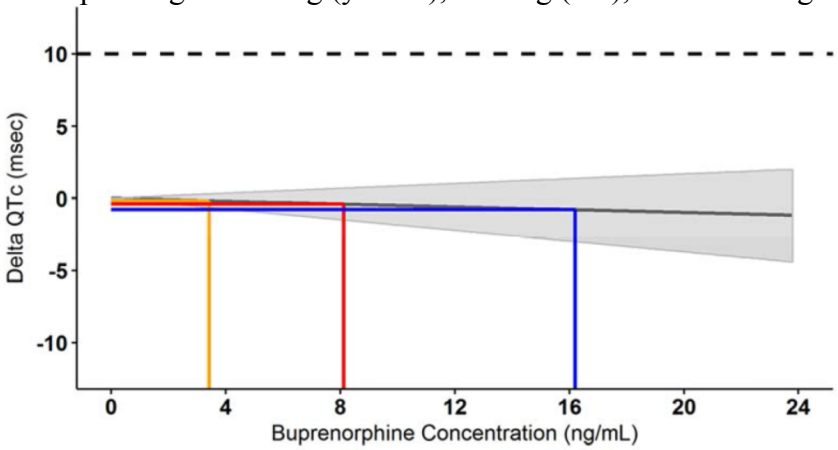
increase in a 70-year old compared to an 18-year old subject), central vs non-central reading (-8.4 msec), sex (+7.6 msec in females), methadone (+6.1 msec), barbiturates (+5.0 msec), phencyclidine (+3.4 msec), hydroxyzine and cocaine (+1.7 msec each), Holter vs non-Holter (-1.7 msec), oxycodone (-1.5 msec), and codeine (+1.3 msec). Alpha was affected by COWS scores only, with an alpha of 0.341 for a COWS score of 5 and 0.363 for a COWS score of 20. The concentration-related slope was non-positive, with a -1.6 msec difference at the highest observed concentration of buprenorphine (32 ng/mL). The 90% CIs for the geometric mean Cmax and the Delta QTc are presented in Table 24 and Figure 23, along with the bias-corrected 90% CI for the Delta QTc. The results from the modeling indicated that upper 90% CI is under 10 msec after multiple RBP-6000 injections, even at 2-fold higher than the proposed dose of 300 mg. In all, RBP-6000 (buprenorphine) impact on QT is insignificant at clinically relevant buprenorphine concentrations, after considering for the covariates that may influence HR and QT in patients with OUD.

Table 24 Mean, median, and 90% confidence intervals for the geometric Cmax and delta QTc (Bootstrap Analysis)

	Geometric Mean C_{max} (ng/mL)			Delta QTc (msec)			
	Mean	Median	90% Confidence Interval	Mean	Median	90% Confidence Interval	Bias- Corrected 90% Confidence Interval
100 mg Q28D	3.44	3.43	3.25 to 3.63	-0.17	-0.16	-0.65 to 0.29	-0.65 to 0.29
300 mg Q28D	8.12	8.12	7.54 to 8.72	-0.40	-0.38	-1.52 to 0.66	-1.52 to 0.67
2X300 mg Q28D	16.2	16.2	15.1 to 17.4	-0.79	-0.75	-3.04 to 1.32	-3.05 to 1.34

Q28D=every 28 days; QTc=corrected QT interval
Source: QT modeling report INDV-6000-Q01, Table 3

Figure 23 Predicted mean (90% confidence interval) Delta QTc at concentration levels corresponding to 100 mg (yellow), 300 mg (red), and 2x300mg RBP-6000 (blue)



Source: QT modeling report INDV-6000-Q01, Figure 5

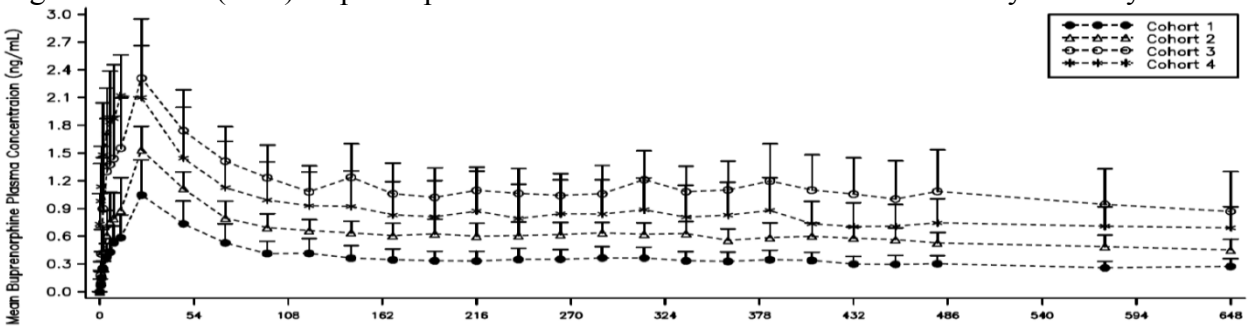
3.3.6 What is the single dose pharmacokinetic information of Sublocade?

Study RB-US-11-0020

Study RB-US-11-0020 evaluated pharmacokinetics of a single dose of 50 mg, 100 mg, 200 mg RBP-6000 SC injection (Cohorts 1, 2, and 3, respectively), and for a single dose of 100 mg RBP-6000 SC injection following a 7-day buprenorphine sublingual stabilization or "lead-in" phase to achieve a stable buprenorphine dose of 12 mg/day in subjects with opioid use disorder (Cohort 4). The following blood samples for buprenorphine and norbuprenorphine were obtained for all cohorts: Day 1 – pre-dose, 0.5, 1, 2, 4, 6, 8, 12 h, Days 2-21 (24-480 h), Days 25, 28, 31, 35, 42, 49, 56, 63, 70, 77, 84, 112, 140 and 150. For Cohort 4, the following additional samples were collected: Days -7 to -1, Day -1 – pre-dose, 0.5, 1, 2, 4, 6, 8 and 12 h. Plasma concentrations of buprenorphine and norbuprenorphine were determined using a previously validated LC-MS/MS assay. The LLOQ was established as 0.0250 ng/mL for buprenorphine and 0.0200 ng/mL for norbuprenorphine.

After a single dose RBP-6000 100 mg SC injection (without buprenorphine sublingual stabilization or "lead-in" phase prior to SC injection), the buprenorphine peak was observed approximately 24 h post administration. Observed buprenorphine levels declined to a plateau until the end of the dosing interval (Day 28; Figure 24; Cohort 2, open-triangle symbol), indicating that buprenorphine is consistently released from the RBP-6000 during the dosing interval.

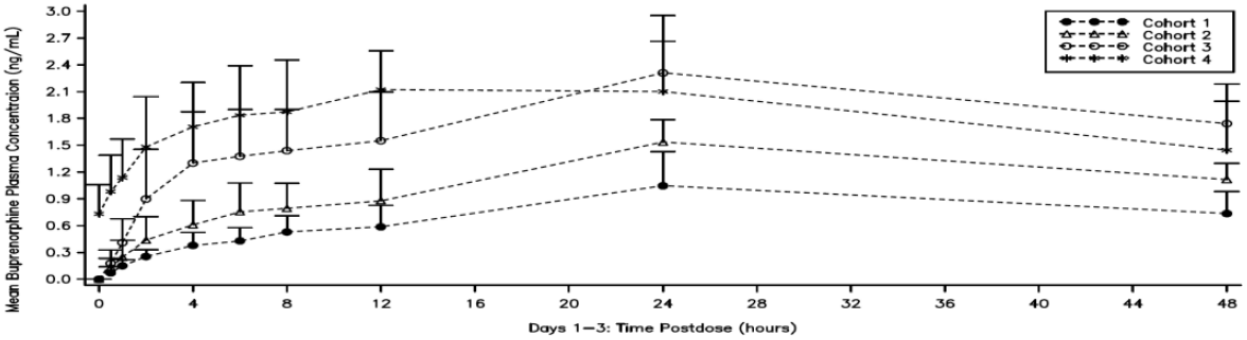
Figure 24 Mean (±SD) Buprenorphine Plasma Concentrations versus Time Day 1 to Day 28



SD = standard deviation
Cohort 1 = a single SC injection of RBP-6000 containing 50 mg buprenorphine.
Cohort 2 = a single SC injection of RBP-6000 containing 100 mg buprenorphine.
Cohort 3 = a single SC injection of RBP-6000 containing 200 mg buprenorphine.
Cohort 4 = QD dosing with SUBOXONE SL, 8 mg (two 4 mg doses approximately 3 hours apart) on Day -7 and 12 mg on Days -6 through -1.
Source: study-report-body.pdf; Figure 7; Figure 14.2.2.1.4 and Table 14.2.1.1

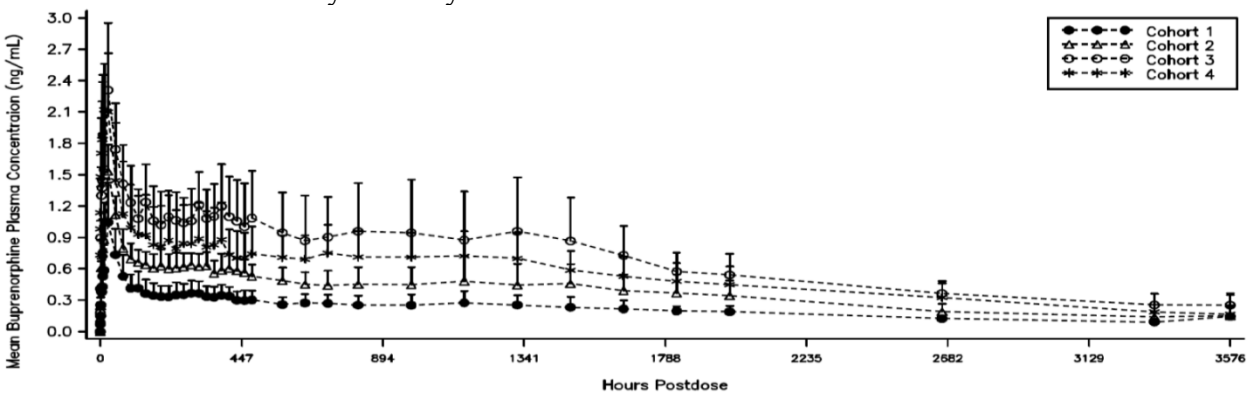
Mean buprenorphine plasma concentration-time data for all cohorts on Days 1-3 are shown in Figure 25. Mean buprenorphine plasma concentration-time data for all cohorts on Days 1-150 are shown on a linear scale in Figure 26.

Figure 25 Plot of Mean (+ SD) Buprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to Day 3



SD = standard deviation
Cohort 1 = a single SC injection of RBP-6000 containing 50 mg buprenorphine.
Cohort 2 = a single SC injection of RBP-6000 containing 100 mg buprenorphine.
Cohort 3 = a single SC injection of RBP-6000 containing 200 mg buprenorphine.
Cohort 4 = QD dosing with SUBOXONE SL, 8 mg (two 4 mg doses approximately 3 hours apart) on Day -7 and 12 mg on Days -6 through -1.
Source: Figure 14.2.2.1.2 and Table 14.2.1.1

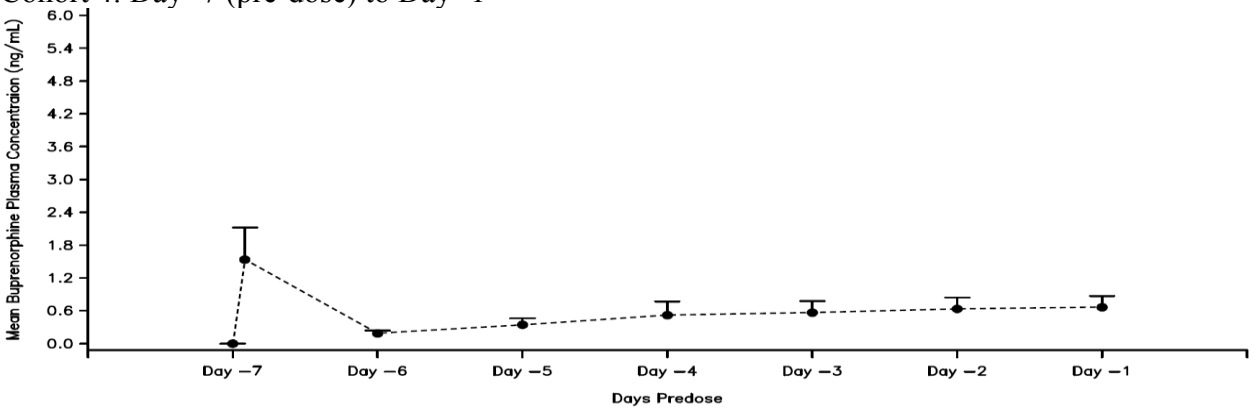
Figure 26 Plot of Mean (+ SD) Buprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to Day 150



SD = standard deviation
Cohort 1 = a single SC injection of RBP-6000 containing 50 mg buprenorphine.
Cohort 2 = a single SC injection of RBP-6000 containing 100 mg buprenorphine.
Cohort 3 = a single SC injection of RBP-6000 containing 200 mg buprenorphine.
Cohort 4 = QD dosing with SUBOXONE SL, 8 mg (two 4 mg doses approximately 3 hours apart) on Day -7 and 12 mg on Days -6 through -1.
Source: Figure 14.2.2.1.3 and Table 14.2.1.1

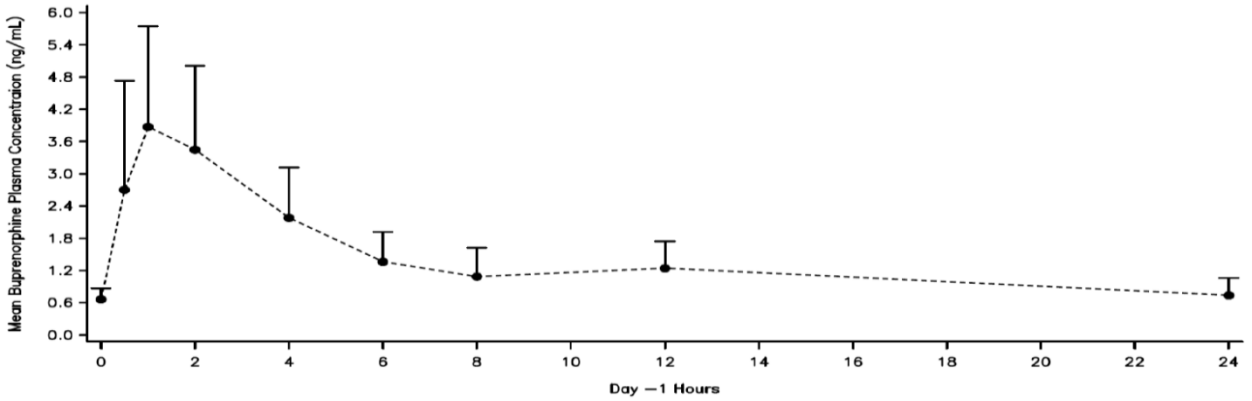
For Suboxone lead-in period in Cohort 4, mean buprenorphine plasma concentration-time data from Days -7 to -1 are shown in Figure 27. Mean buprenorphine plasma concentration-time data for Cohort 4 on Day -1 only are shown in Figure 28.

Figure 27 Plot of Mean (+ SD) Buprenorphine Concentrations versus Time on a Linear Scale for Cohort 4: Day -7 (pre-dose) to Day -1



SD = standard deviation
Cohort 4 = QD dosing with SUBOXONE SL, 8 mg (two 4 mg doses approximately 3 hours apart) on Day -7 and 12 mg on Days -6 through -1.
Source: Figure 14.2.2.1.1, Figure 14.2.2.2.1, and Table 14.2.1.2

Figure 28 Plot of Mean (± SD) Buprenorphine Concentrations versus Time on a Linear Scale for Cohort 4: Day -1



SD = standard deviation
Cohort 4 = QD dosing with SUBOXONE SL, 8 mg (two 4 mg doses approximately 3 hours apart) on Day -7 and 12 mg on Days -6 through -1.
Source: Figure 14.2.2.1.1, Figure 14.2.2.2.1, and Table 14.2.1.1

Buprenorphine pharmacokinetic parameters are presented in Table 25.

Table 25 Buprenorphine pharmacokinetic parameters from a single dose RBP-6000 50, 100 and 200 mg in Study RB-US-11-0020 (note: Cohort 2: 100 mg)

Parameter	Statistic	RBP-6000 alone			RBP-6000 + Suboxone SL
		Cohort 1 50 mg	Cohort 2 100 mg	Cohort 3 200 mg	Cohort 4 100 mg
Cavg (ng/mL)	n	12	12	12	10
	Mean	0.370	0.633	1.138	0.951
	%CV	27.4	16.6	25.7	32.5
Cmax (ng/mL)	n	12	12	12	12
	Mean	1.051	1.537	2.427	2.285
	%CV	35.6	16.4	20.9	23.2
Cmin (ng/mL)	n	12	12	12	12
	Mean	0.059	0.089	0.148	0.275
	%CV	56.1	44.3	67.8	64.3
Tmax (hr)	n	12	12	12	12
	Median	24.0	24.0	24.0	18.0
	Min, Max	4.00, 24.03	24.0, 48.0	4.00, 144.0	4.00, 24.0

%CV = coefficient of variation; hr = hour; Max = maximum; Min = minimum; PK = pharmacokinetic; QD = once daily; SC = subcutaneous;
SD = standard deviation; SL = sublingual
Cohort 1 = a single SC injection of RBP-6000 containing 50 mg buprenorphine.
Cohort 2 = a single SC injection of RBP-6000 containing 100 mg buprenorphine.
Cohort 3 = a single SC injection of RBP-6000 containing 200 mg buprenorphine.
Cohort 4 = QD dosing with SUBOXONE SL, 8 mg (two 4 mg doses approximately 3 hours apart) on Day -7 and 12 mg on Days -6 through -1.
Source: Table 14.2.1.3, Listing 16.2.6.2.1, Listing 16.2.6.2.2, and Listing 16.2.6.2.3

In the overall profile, median tmax was 24 hours for Cohorts 1-3 and 18 hours for Cohort 4. CL/F was fairly constant at the 3 dose levels of 50 mg, 100 mg, and 200 mg. Vd/F increased with the increase in RBP-6000 dose from 50 mg to 200 mg in Cohorts 1-3. For buprenorphine, mean t½ after RBP-6000 injection increased slightly with the increase in dose from 50 mg to 200 mg (1078 hours [Day 45] at 50 mg, 1376 hours [Day 57] at 100 mg, and 1573 hours [Day 66] at 200 mg). Overall, percent fluctuation was similar between all the cohorts. Swing increased with the dose in Cohorts 1-3, while the lowest swing value was observed in Cohort 4.

3.3.7 What is the multiple dose pharmacokinetic information of Sublocade?

Multiple dose

Study RB-US-12-0005 was an open-label, multicenter study which evaluated pharmacokinetics of multiple dose Sublocade injections in adult subjects seeking treatment for opioid dependence previously on buprenorphine SL treatment. Subjects were stabilized over a 13-day period on various doses of Subutex SL tablets followed by 50, 100, 200 mg or 300 mg Sublocade multiple dose injections (Table 26). Subjects who received either 200 or 300 mg Sublocade and reached 4 or 6 injections, respectively, will have an option to a positron emission tomography (PET) sub-study, which assessed in opioid receptor binding information; two subjects participated in the PET pilot sub-study: 1 subject received 12 SC injections of 200 mg, and 1 subject received 6 SC injections of 300 mg. The PET scans (utilizing [^{11}C]carfentanil) were conducted at 7 days and 28 days post-dose following the 12th SC injection for the first subject who received 200 mg, and the

6th SC injection for the second subject who received 300 mg. Information obtained from the PET sub-study from these two subjects is described in conjunction with opioid receptor binding discussion. The reviewer is referred to Pharmacometric's review regarding opioid receptor binding discussion.

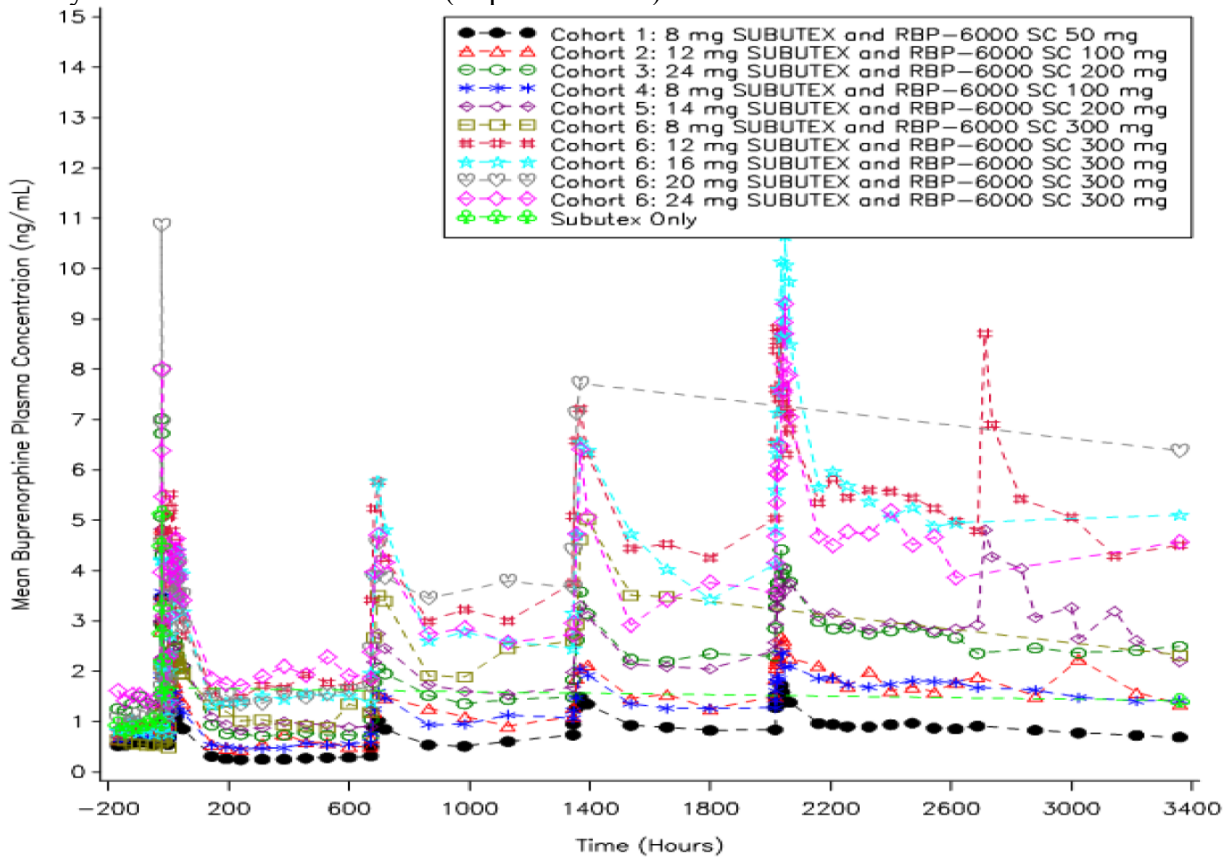
Table 26 Sublocade treatment doses cohorts Subutex SL lead-in phase

	Cohort									
	1	2	3	4	5	6				
Subutex SL (mg)	8	12	24	8	14	8	12	16	20	24
Sublocade (mg)	50	100	200	100	200	300				
	4 Sublocade injections at 28-day intervals					Up to 6 Sublocade injections at 28-day intervals				

The following blood samples for buprenorphine and norbuprenorphine were obtained for Cohorts 1-5: Days -7 to -1 (pre-dose Subutex), Day -1 – pre-dose, 0.5, 1, 2, 4, 6, 8, 12, Day 1 (1st injection) – pre-dose, 1, 2, 4, 6, 8, 12h, Day 2 – 20, 24, 25, 26, 28, 30, 32, 36 h; Days 3, 7, 9, 11, 14, 17, 20, 23, 26; Day 29 (2nd injection) – 1 and 12 h, Days 30, 31, 37, 42, 48; Day 57 (3rd injection) – 1 and 12 h, Days 58, 59, 65, 70, 76; Day 85 (4th injection) – pre-dose, 1, 2, 4, 6, 8, 12 h, Day 86 – 20, 24, 25, 26, 28, 30, 32, 36 h, Day 87 – 44, 48 h, Days 91, 93, 95, 98, 101, 104, 107, 110, 113, 121, 127, 135, 141. For Cohort 6: same timepoints as Cohorts 1-5 up to 3rd injections; Day 85 (4th injection) – pre-dose, 1, 2, 4, 6, 8, 12 h, Day 86 – 20, 24, 25, 26, 28, 30, 32, 36 h, Day 87 – 44, 48 h, Days 91, 93, 95, 98, 101, 104, 107, 110; Day 113 (5th injection) – 114, 115, 121, 126, 132; Day 141 (6th injection) – pre-dose, 1, 2, 4, 6, 8, 12h, Day 142 – 20, 24, 25, 26, 28, 30, 32, 36 h, Day 143 – 44, 48, Days 147, 149, 151, 154, 157, 160, 163, 166, 169, 177, 183, 191, 197.

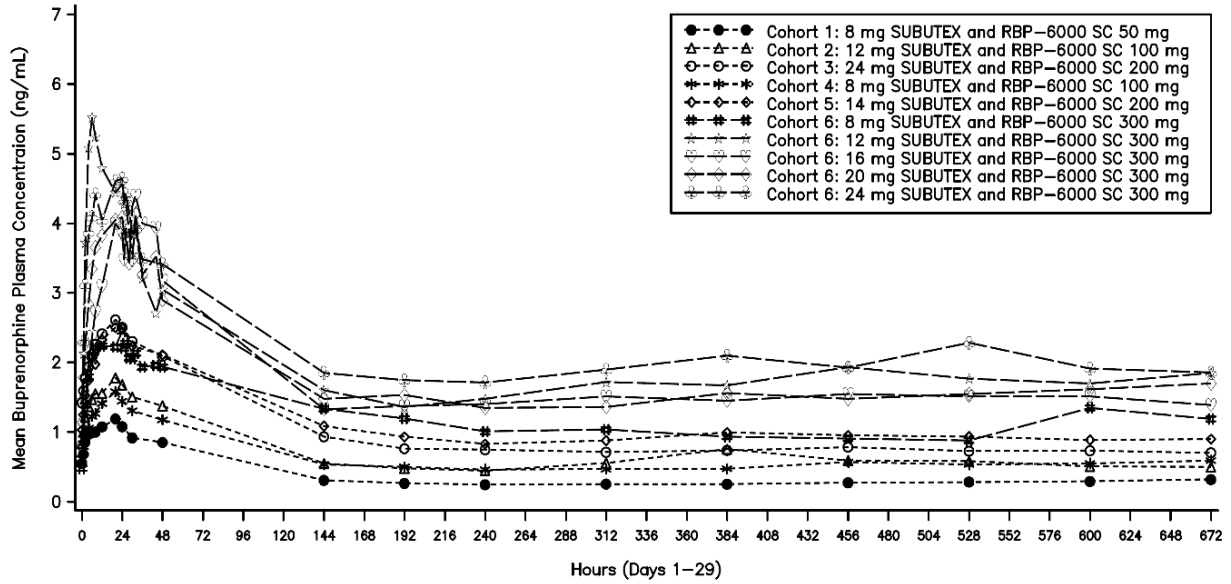
Mean buprenorphine plasma concentration-time profiles for all cohorts are shown in Figure 29. Mean buprenorphine plasma concentration-time profiles for all cohorts for separate Injections 1, 2, 3, and 4 are shown in Figures 30, 31, 32, and 33 respectively.

Figure 29 Mean buprenorphine plasma concentrations by scheduled sampling time for all cohorts on Days -7 to 141 on a linear scale (Population: PK)



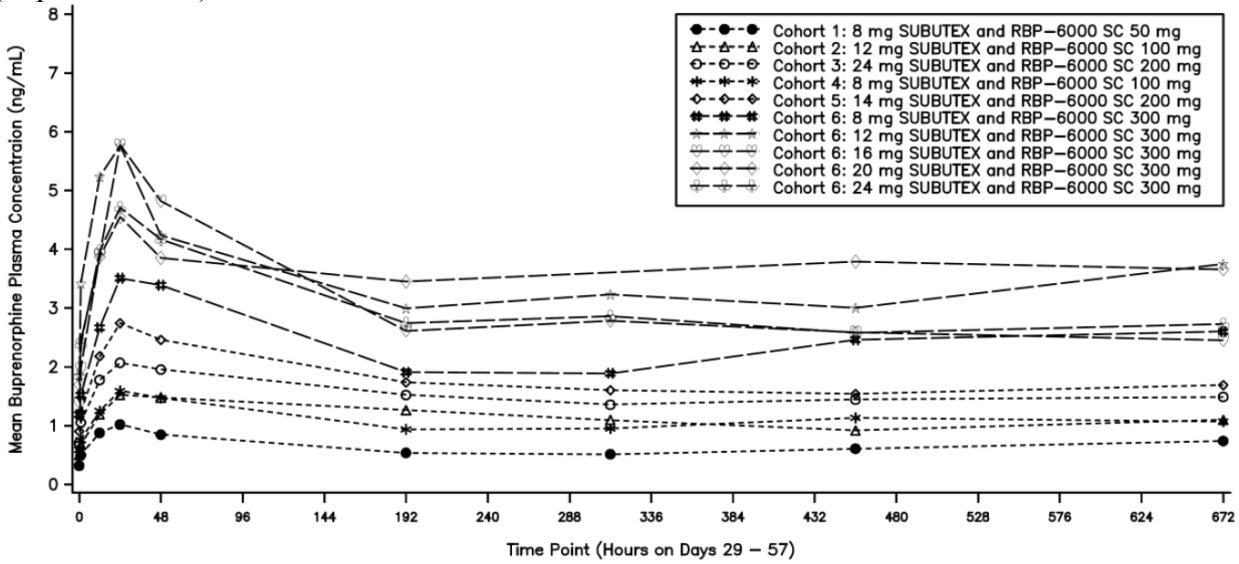
Source: Figure 14.2.2.1.7 and Table 14.2.1.1.

Figure 30 Mean buprenorphine plasma concentrations versus time post RBP-6000 SC Injection 1 from study Day 1 to Day 29 (672 h) (Population: PK)



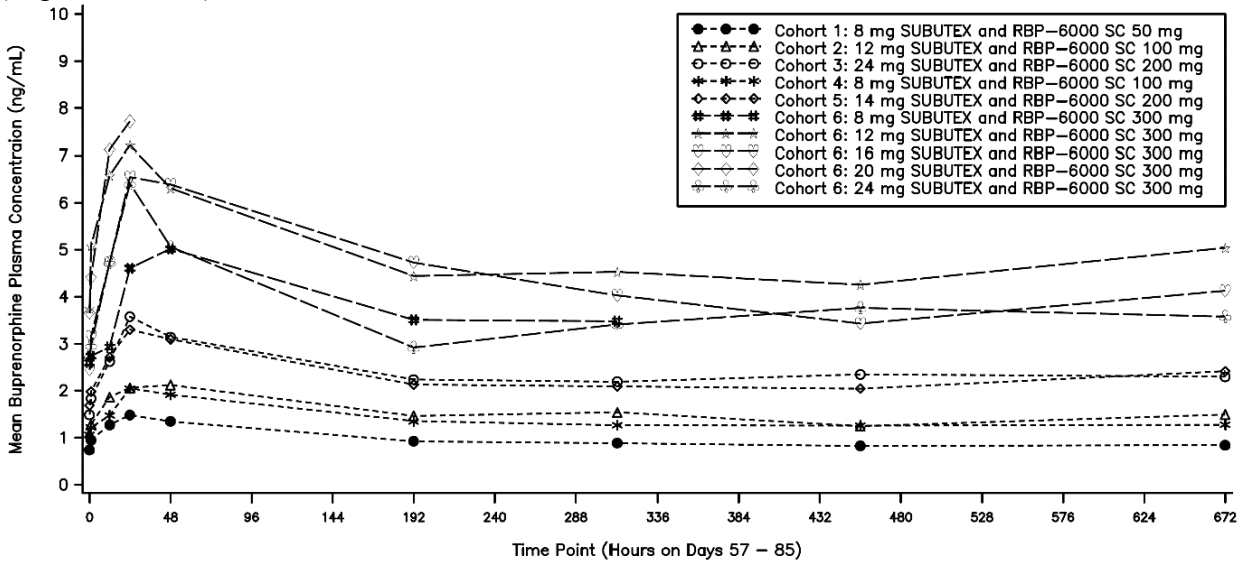
Source: Figure 14.2.2.1.2b and Table 14.2.1.1.

Figure 31 Mean buprenorphine plasma concentrations versus time post RBP-6000 SC Injection 2 from study Day 29 to Day 57 (672 h)
(Population: PK)



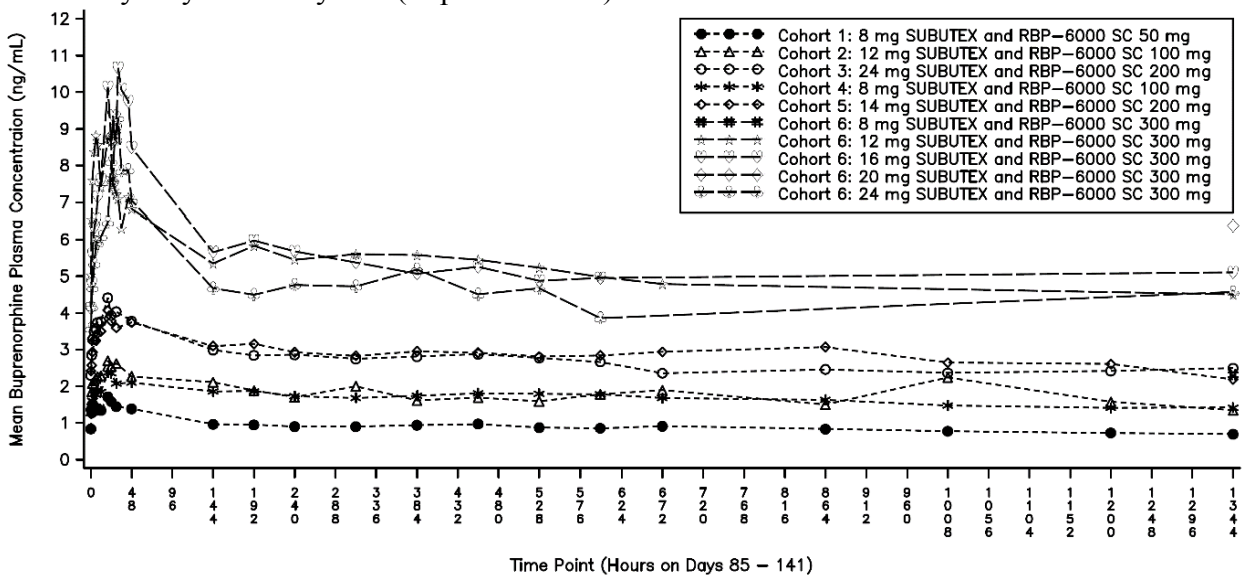
SouSource: Figure 14.2.2.1.3 and Table 14.2.1.1.

Figure 32 Mean buprenorphine plasma concentrations versus time post RBP-6000 SC Injection 3 from study Day 57 to Day 85 (672 h)
(Population: PK)



Source: Figure 14.2.2.1.4 and Table 14.2.1.1.

Figure 33 Mean buprenorphine plasma concentrations versus time post RBP-6000 SC Injection 4 from study Day 85 to Day 141 (Population: PK)



Source: Figure 14.2.2.1.5 and Table 14.2.1.1.

Summary of PK parameters for the overall phase for buprenorphine is provided in Table 27.

Table 27 Buprenorphine Plasma Pharmacokinetic Parameters Summary – Overall Phase (Population: PK) separated by injection days, Day 1 (Injection 1), Day 85 (Injection 4) and Day 141 (Injection 6)

			SUBUTEX SL; RBP-6000					
Parameter	**Time point**	**Statistic**	**Cohort 1 8 mg; 50 mg**	**Cohort 2 12 mg; 100 mg**	**Cohort 3 24 mg; 200 mg**	**Cohort 4 8 mg; 100 mg**	**Cohort 5 14 mg; 200 mg**	**Cohort 6 Total; 300 mg**
AUC 0-24 (OVR) (hr*ng/mL)	DAY 1 DOSE	n	15	15	14	15	12	14
		Mean	24.922	36.981	55.291	31.747	50.034	85.090
		SD	6.4450	14.3565	17.0179	13.2180	11.4899	28.7163
		%CV	25.9	38.8	30.8	41.6	23.0	33.7
		Median	24.278	36.699	52.430	30.173	47.181	86.170
		Min,Max	13.02, 35.31	13.96, 65.84	32.63, 93.06	15.89, 65.49	35.11, 72.78	30.17, 128.93
		Geometric Mean	24.091	34.334	53.082	29.496	48.901	79.886
AUCtau (hr*ng/mL)	DAY 1 DOSE	n	15	14	13	14	14	11
		Mean	246.650	461.366	642.010	413.438	756.053	1268.012
		SD	54.9881	142.2166	228.0284	133.0365	223.8099	389.6719
		%CV	22.3	30.8	35.5	32.2	29.6	30.7
		Median	256.246	451.168	602.314	388.270	694.699	1131.870
		Min,Max	148.95, 363.20	273.04, 723.10	381.93, 1226.09	210.95, 655.34	426.71, 1150.73	889.92, 1995.21
		Geometric Mean	240.620	442.112	610.630	394.190	726.666	1218.902
Cavg (ng/mL)	DAY 1 DOSE	n	15	14	13	14	14	11
		Mean	0.367	0.687	0.955	0.615	1.125	1.887
		SD	0.0818	0.2116	0.3393	0.1980	0.3331	0.5799
		%CV	22.3	30.8	35.5	32.2	29.6	30.7
		Median	0.381	0.671	0.896	0.578	1.034	1.684
		Min,Max	0.22, 0.54	0.41, 1.08	0.57, 1.82	0.31, 0.98	0.63, 1.71	1.32, 2.97
		Geometric Mean	0.358	0.658	0.909	0.587	1.081	1.814
Cmax (OVR) (ng/mL)	DAY 1 DOSE	n	15	15	14	15	15	14
		Mean	1.352	2.023	2.732	1.686	2.861	4.817
		SD	0.4641	0.8251	0.7866	0.6200	0.7136	1.4337
		%CV	34.3	40.8	28.8	36.8	24.9	29.8
		Median	1.280	1.850	2.570	1.530	2.670	4.750
		Min,Max	0.66, 2.61	0.94, 3.74	1.71, 4.61	0.87, 3.14	1.80, 4.11	2.41, 6.74
		Geometric Mean	1.287	1.870	2.638	1.588	2.781	4.604
Cmin (OVR) (ng/mL)	DAY 1 DOSE	n	15	15	14	15	15	14
		Mean	0.206	0.375	0.589	0.410	0.700	0.836
		SD	0.0556	0.1001	0.2522	0.1955	0.2196	0.3756
		%CV	27.0	26.7	42.8	47.6	31.4	44.9
		Median	0.207	0.381	0.497	0.344	0.626	0.860
		Min,Max	0.09, 0.30	0.23, 0.65	0.30, 1.29	0.17, 0.87	0.40, 1.12	0.40, 1.71
		Geometric Mean	0.198	0.364	0.548	0.375	0.670	0.762
Tmax (OVR) (hr)	DAY 1 DOSE	n	15	15	14	15	15	14
		Mean	15.470	47.078	18.720	24.933	21.072	17.429
		SD	6.2117	102.4253	7.6313	13.1555	10.7949	11.0225
		%CV	40.2	217.6	40.8	52.8	51.2	63.2
		Median	20.000	20.000	20.000	20.000	20.000	20.000
		Min,Max	4.00, 20.05	4.00, 414.17	6.00, 30.00	4.00, 48.00	6.00, 48.00	4.00, 32.00
		Geometric Mean	13.709	20.533	16.981	21.513	18.198	13.500

AUC 0-24 (OVR) (hr*ng/mL)	DAY 85 DOSE	n	11	12	11	10	8	7
		Mean	35.250	56.231	91.197	47.633	81.417	178.109
		SD	14.5405	15.6411	27.4005	9.6147	18.3829	43.2176
		%CV	41.2	27.8	30.0	20.2	22.6	24.3
		Median	30.331	54.655	82.736	46.181	77.622	171.460
		Min,Max	22.07, 70.47	27.77, 83.29	60.57, 140.20	34.38, 62.71	61.15, 112.41	122.16, 255.64
		Geometric Mean	33.131	54.058	87.698	46.767	79.666	173.784
AUCtau (hr*ng/mL)	DAY 85 DOSE	n	10	11	9	8	7	2
		Mean	667.611	1272.047	1932.068	1275.098	2051.989	3230.873
		SD	254.2712	434.1013	455.1540	252.8500	466.6935	430.6718
		%CV	38.1	34.1	23.6	19.8	22.7	13.3
		Median	652.871	1252.517	1713.514	1341.354	1929.187	3230.873
		Min,Max	318.33, 1070.70	854.45, 2406.25	1445.06, 2713.9	770.77, 1583.65	1665.06, 3025.55	2926.34, 3535.40
		Geometric Mean	622.695	1217.720	1887.775	1249.045	2013.339	3216.489
Cavg (ng/mL)	DAY 85 DOSE	n	10	11	9	8	7	2
		Mean	0.993	1.893	2.875	1.897	3.054	4.808
		SD	0.3784	0.6460	0.6773	0.3763	0.6945	0.6409
		%CV	38.1	34.1	23.6	19.8	22.7	13.3
		Median	0.972	1.864	2.550	1.996	2.871	4.808
		Min,Max	0.47, 1.59	1.27, 3.58	2.15, 4.04	1.15, 2.36	2.48, 4.50	4.35, 5.26
		Geometric Mean	0.927	1.812	2.809	1.859	2.996	4.786
Cmax (OVR) (ng/mL)	DAY 85 DOSE	n	11	12	11	10	11	7
		Mean	2.085	3.066	4.526	2.554	4.404	9.637
		SD	1.4381	0.8658	1.3078	0.4775	0.9231	2.3409
		%CV	69.0	28.2	28.9	18.7	21.0	24.3
		Median	1.650	2.935	4.230	2.405	4.040	9.840
		Min,Max	1.10, 6.26	2.01, 5.07	2.88, 6.64	2.10, 3.43	3.02, 6.16	6.46, 12.60
		Geometric Mean	1.835	2.964	4.360	2.517	4.317	9.383
Cmin (OVR) (ng/mL)	DAY 85 DOSE	n	11	12	11	10	11	7
		Mean	0.557	1.263	2.121	1.180	2.256	4.043
		SD	0.1559	0.3574	0.4689	0.2803	0.6472	0.6936
		%CV	28.0	28.3	22.1	23.8	28.7	17.2
		Median	0.606	1.220	2.240	1.205	2.370	3.820
		Min,Max	0.29, 0.78	0.75, 1.94	1.38, 2.74	0.83, 1.74	1.24, 3.13	3.04, 5.19
		Geometric Mean	0.535	1.216	2.071	1.151	2.166	3.992
Tmax (OVR) (hr)	DAY 85 DOSE	n	11	12	11	10	11	7
		Mean	18.727	60.082	23.470	75.387	26.182	21.429
		SD	5.6761	94.6239	7.1642	160.2744	15.4261	11.8161
		%CV	30.3	157.5	30.5	212.6	58.9	55.1
		Median	20.000	20.000	20.083	24.000	24.000	24.000
		Min,Max	2.00, 24.00	12.00, 315.95	8.00, 30.08	4.00, 529.83	4.00, 48.00	4.00, 36.00
		Geometric Mean	16.494	31.181	22.140	28.254	21.213	17.280
AUC 0-24 (OVR) (hr*ng/mL)	DAY 141 DOSE	n						1
		Mean						155.779
		SD						.
		%CV						.
		Median						155.779
		Min,Max						155.78, 155.78
		Geometric Mean						155.779

AUCtau (hr*ng/mL)	DAY 141 DOSE	n					2	
		Mean					2585.976	
		SD					276.6695	
		%CV					10.7	
		Median					2585.976	
		Min,Max					2390.34, 2781.61	
		Geometric Mean					2578.566	
Cavg (ng/mL)	DAY 141 DOSE	n					2	
		Mean					3.848	
		SD					0.4117	
		%CV					10.7	
		Median					3.848	
		Min,Max					3.56, 4.14	
		Geometric Mean					3.837	
Cmax (OVR) (ng/mL)	DAY 141 DOSE	n					2	1
		Mean					5.015	7.140
		SD					0.8980	
		%CV					17.9	
		Median					5.015	7.140
		Min,Max					4.38, 5.65	7.14, 7.14
		Geometric Mean					4.975	7.140
Cmin (OVR) (ng/mL)	DAY 141 DOSE	n					2	1
		Mean					2.910	4.290
		SD					0.7354	
		%CV					25.3	
		Median					2.910	4.290
		Min,Max					2.39, 3.43	4.29, 4.29
		Geometric Mean					2.863	4.290
Tmax (OVR) (hr)	DAY 141 DOSE	n					2	1
		Mean					24.000	24.350
		SD					0.0000	
		%CV					0.0	
		Median					24.000	24.350
		Min,Max					24.00, 24.00	24.35, 24.35
		Geometric Mean					24.000	24.350

Subjects were dosed with SUBUTEX SL tablet followed by SC injections of RBP-6000 containing buprenorphine.
The Cohort 6 column is the total for the 8 mg, 12 mg, 16 mg, 20 mg, and 24 mg SUBUTEX columns from Table 14.2.1.3.
Source: Table 14.2.1.3

Injection 1(Day 1)

Following Injection 1, buprenorphine exposure increased with the increase in the dose of Sublocade. Subutex SL "lead-in" phase may have some influence in the buprenorphine levels as buprenorphine exposure increased within the same Sublocade dose group (Cohort 6).

The observed median Tmax was 20 hours for Cohorts 1-5. For Cohort 6, it ranged from 6 to 28 h (median Tmax: 20, 6, 28, 26, 12h, for 6 8, 12, 16, 20, 24 mg Subutex lead-in dose groups, respectively); note that there are limited number of subjects in Cohort 6.

Injection 4 (Day 85)

Following Injection 4, the previous Subutex lead-in phase would not influence the buprenorphine exposure due to 4 months of time lapse since the Injection 1, thus, the buprenorphine exposure would solely from Sublocade injection. Buprenorphine exposure increased with the increase in the dose of Sublocade. The observed median Tmax was 20 to 24 h for Cohorts 1-5. For Cohort

6, it ranged from 8 to 34 h (median Tmax: 8, 34, 25h, for 12, 16, 24 mg Subutex lead-in dose groups, respectively); again, note that there are limited number of subjects in Cohort 6.
Compared to Injection 1, the buprenorphine exposure was higher, as there appeared to be some apparent accumulation of buprenorphine at Injection 4 ([Rac(AUCtau)] and [Rac (Cmax)] ratios were consistently greater than 1 and ranged from 2.400 to 3.550 and 1.316 to 2.427, respectively, across the dose range).

Injection 6 (Day 141)
Only 3 subjects not participating in the PET imaging sub-study received more than 4 SC injections of RBP-6000 (2 subjects in 14 mg/200 mg Subutex/Sublocade dose, Cohort 5; and 1 subject in 12 mg/300 mg Subutex/Sublocade dose, Cohort 6). Due to limited number of subjects, the results from the Injection 6 may be difficult to assess fully and drawing a conclusion from Injection 6 information should be interpret with caution.

Steady-state attainment

Steady-state assessment of buprenorphine for the Sublocade doses of 50 mg, 100 mg, 200 mg, and 300 mg was carried out using Helmert's transformation method within an ANOVA, with the natural log-transformed Ctrough concentrations (using pre-dose concentration for Day 1) as the dependent variable with day as the fixed effect (a series of contrasts compared the mean Ctrough value of the first day to the pooled mean over all remaining time points for each dose level; the second contrast compared the mean Ctrough value at the second day to the pooled mean over all remaining time points for each dose level; testing continued until the contrast was not statistically significant at the 0.1 level). The first time point at which the comparison was not significant was the dosing interval at which steady-state was attained. The Ctrough values of Days 29, 57, 85, and 113 were used the Helmert transformation as described.

Attainment of steady-state for buprenorphine following RBP-6000 SC dosing from Day 1 to Day 85 (Day 141 for the 200 mg and 300 mg groups only) was assessed based on the first instance of non-significant contrast comparison.

Following SC injections of RBP-6000, steady-state levels of buprenorphine were achieved by the Injection 3 (Day 57) in the 50 mg dose group, by the Injection 4 (Day 85) in the 300 mg dose group, and by the Injection 6 (Day 141) for the 200 mg dose group. Steady-state was not achieved for the 100 mg dose group based on the data for 4 SC injections, based on the statistical analysis (Table 28).

Table 28 Assessment of Steady-State of RBP-6000 – (Population: PK)

RBP-6000	Day	N	Geometric LS Means	% Ratio of Geometric LS Means	p-value	90% CI of the Ratio (%)
50 mg	Day 29	15	0.30	39.2	<0.001	(31.8, 48.3)
	Day 57	12	0.68	82.8	0.200a	(64.9, 105.6)
	Day 85	11	0.80	96.0	0.815	(71.6, 128.7)
	Day 113	10	0.83			
100 mg	Day 29	27	0.52	39.2	<0.001	(34.9, 44.0)
	Day 57	24	1.05	69.8	<0.001	(61.3, 79.5)
	Day 85	22	1.35	81.3	0.033	(69.4, 95.3)
	Day 113	19	1.66			
200 mg	Day 29	27	0.76	30.7	<0.001	(27.0, 35.0)
	Day 57	24	1.53	54.8	<0.001	(47.2, 63.6)
	Day 85	22	2.28	76.3	0.013	(64.0, 91.1)
	Day 113	16	2.53	78.1	0.088	(61.6, 99.1)
	Day 141	3	3.00	85.9	0.537a	(57.3, 129.0)
	Day 169	3	3.49			
300 mg	Day 29	11	1.55	36.0	<0.001	(28.1, 46.1)
	Day 57	10	2.92	61.5	0.007	(46.5, 81.5)
	Day 85	7	4.23	86.0	0.472 a	(60.6, 122.2)
	Day 113	2	4.70	93.5	0.834	(54.3, 161.0)
	Day 141	2	5.41	115.7	0.730	(56.8, 235.7)
	Day 169	1	4.68			

Subjects were dosed with SUBUTEX SL tablet followed by SC injections of RBP-6000 containing buprenorphine.
An analysis of variance (ANOVA) was performed with the natural log-transformed Ctrough values as the dependent variable with day as fixed effect. Ratio was for comparing the geometric mean concentration of the corresponding study day to the geometric mean concentration pooled over all remaining days.
p-value was for testing if the corresponding ratio of geometric LS means was 1.
a This was the first non-significant comparison at the 0.1 level.
Source: Table 14.2.1.7a

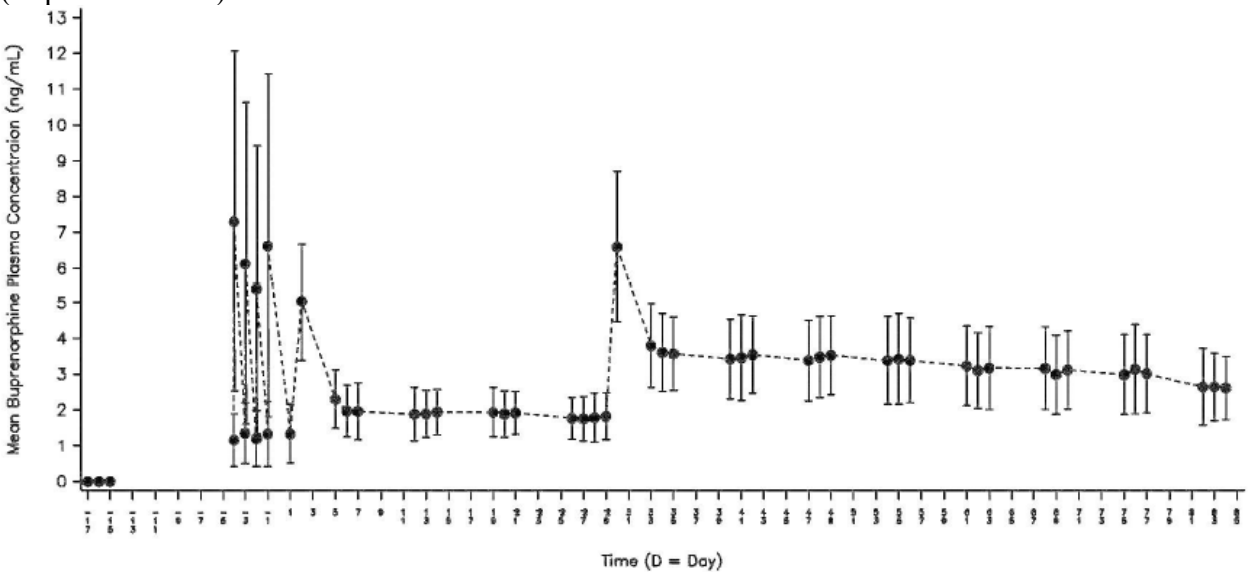
For Subutex tablet administration prior to RBP-6000 doses, results show that buprenorphine achieved steady state by Day -7 in all dose groups except for the 12 mg dose for which steady-state was achieved on Day -6 (Table 26).

Study RB-US-13-0002 – opioid blockade study

Study RB-US-13-0002 was a double-blind, placebo-controlled, two of Sublocade 300 mg injections (28-day apart; Day 1 and Day 29) study in non-treatment-seeking subjects with moderate to severe OUD to assess the blockade of hydromorphone's subjective effects. Patients were treated with up to 24 mg Suboxone in the lead-in phase. Buprenorphine blood samples were collected at: Day 1 – pre-dose, Days 2, 5-7, 12-14, 19-21, 26-28, Day 29 – pre-dose, Days 30, 33-35, 40-42, 47-49, 54-56, 61-63, 68-70, 75-77, and 82-84. The primary objective was to assess "Drug Liking" scores measured after challenge with 6mg or 18mg of intramuscular (IM) hydromorphone with placebo.

Mean buprenorphine plasma concentration-time curve is shown in Figure 34.

Figure 34 Mean (±SD) Buprenorphine Plasma Concentrations versus Time on a Linear Scale (Population: ITT)



D = day; ITT = intent-to-treat; SD = standard deviation
Source: Figure 14.2.2.1.1.1, Table 14.2.1.1, 14.2.1.2, and 14.2.1.3

Following SC RBP-6000 administration, mean buprenorphine plasma concentrations were slightly higher following the second dose on Day 29 when compared with the first dose on Day 1 (Table 29). For individual buprenorphine concentrations observed in Days 5-7, 12-14, 19-21, 26-28 are presented in Table 30.

Table 29 Day 1 (0, 24h) and Day 29 (0 and 24h) time-points plasma concentrations Summary-RBP-6000 (Population: ITT)

Analyte (unit)	Day	Time (hr)	Statistic	RBP-6000 300 mg
Buprenorphine (ng/mL)	Day 1	0	N	37
			Mean (SD)	1.330 (0.8245)
			%CV	62.0
			Median	1.240
			Min, Max	0.154, 3.72
			Geometric Mean	1.073
	Day 2	24	N	38
			Mean (SD)	5.034 (1.6401)
			%CV	32.6
			Median	4.520
			Min, Max	2.89, 11.3
			Geometric Mean	4.815
	Day 29	0	N	30
			Mean (SD)	1.823 (0.6524)
			%CV	35.8
			Median	1.620
			Min, Max	0.975, 3.93
			Geometric Mean	1.725
	Day 30	24	N	30
			Mean (SD)	6.591 (2.1188)
			%CV	32.1
			Median	6.465
			Min, Max	3.69, 13.4
			Geometric Mean	6.289

Table 30 Observed buprenorphine concentrations (ng/mL) on Days 5-7, 12-14, 19-21, 26-28

Parameter	Day 05	Day 06	Day 07	Day 12	Day 13	Day 14	Day 19	Day 20	Day 21	Day 26	Day 27	Day 28
N	38	37	37	36	35	34	33	33	33	30	30	29
Mean	2.30	1.97	1.96	1.88	1.89	1.94	1.93	1.88	1.91	1.77	1.75	1.79
SD	0.81	0.72	0.79	0.74	0.65	0.63	0.68	0.64	0.60	0.58	0.62	0.68
Min	0.10	0.78	0.74	0.71	0.69	0.83	0.74	0.73	0.86	1.07	0.98	1.03
Max	4.65	3.70	4.03	4.70	3.51	3.58	4.34	3.87	3.59	3.82	3.86	3.89

The observed buprenorphine concentrations on Days 5 to 28 after the 1st injection ranged from 1.75 to 2.3 ng/mL. As depicted in Figure xx, the buprenorphine concentrations after 2nd injection appear to be above 2 ng/mL from Days 29 to 84.

3.3.8 What is the relative bioavailability of Sublocade?

In Study RB-US-11-0005, pharmacokinetics for multiple doses of Sublocade 100 mg and 300 mg after buprenorphine sublingual stabilization or "lead-in" phase were evaluated in subjects with opioid use disorder. After 100 and 300 mg multiple SC injections (with Subutex SL tablet stabilization or "lead-in" phase prior to SC injection), with-in study comparison was assessed between single and repeat doses of Sublocade. Sublocade is proposed for use in patients who have undergone buprenorphine stabilization prior to RBP-6000 SC injection; therefore, observed systemic buprenorphine concentrations from the "lead-in" buprenorphine SL daily administration phase to RBP-6000 SC injections were compared.

Observed buprenorphine concentrations, specifically for comparison of Cavg,ss, Cmax,ss, and Cmin,ss, from "lead-in" Subutex SL tablet (i.e., immediately before the first Sublocade injection) are presented in Table 31. Observed buprenorphine concentrations from Sublocade SC injections are presented in Table 32.

Table 31 Observed steady-state buprenorphine concentrations from lead-in sublingual Subutex before first RBP-6000 injection of 100 and 300 mg dose

Parameter	Statistic	Subutex/ RBP-6000 8mg/ 100mg[1]	Subutex/ RBP-6000 12mg /100mg[2]	Subutex/ RBP-6000 8mg/ 300mg[3]	Subutex/ RBP-6000 12mg/ 300mg[3]	Subutex/ RBP-6000 16mg/ 300mg[3]	Subutex/ RBP-6000 20mg/ 300mg[3]	Subutex/ RBP-6000 24mg/ 300mg[3]
Cavg,ss	N	15	15	3	4	2	2	3
	Mean	1.251	1.707	0.837	1.782	1.666	2.754	2.907
	SD	0.5362	0.5284	0.2888	0.7419	0.8231	1.1887	0.3635
Cmax,ss	N	15	15	3	4	2	2	3
	Mean	3.964	5.350	2.417	4.77	4.265	10.86	8.267
	SD	1.9131	1.7340	1.1794	1.0576	2.1991	4.5821	1.9868
Cmin,ss	N	15	15	3	4	2	2	3
	Mean	0.568	0.806	0.482	0.777	0.763	1.134	1.543
	SD	0.2367	0.3638	0.0854	0.36	0.5056	0.2772	0.2566

1: Cohort 4 Subutex/RBP-6000 8mg/100mg
2: Cohort 2 Subutex/RBP-6000 12mg/100mg
3: Cohort 6 Subutex/RBP-6000 8mg/300mg, 12mg/300mg, 16mg/300mg, 20mg/300mg, 24mg/300mg
SD: standard deviation

Table 32 Observed buprenorphine concentrations after first, fourth and sixth RBP-6000 subcutaneous injections for 100 and 300 mg doses

Parameter	Inj. #	Statistic	Subutex/ RBP-6000 8mg/ 100mg[1]	Subutex/ RBP-6000 12mg/ 100mg[2]	Subutex/ RBP-6000 8mg/ 300mg[3]	Subutex/ RBP-6000 12mg/ 300mg[3]	Subutex/ RBP-6000 16mg/ 300mg[3]	Subutex/ RBP-6000 20mg/ 300mg[3]	Subutex/ RBP-6000 24mg/ 300mg[3]
Cavg,ss	1	N	14	14	1	3	2	2	3
		Mean	0.615	0.687	1.45	1.89	1.76	1.78	2.19
		SD	0.1980	0.2116	.	0.94	0.17	0.13	0.72
	4	N	8	11		2			
		Mean	1.897	1.893		4.81			
		SD	0.3763	0.646		0.64			
Cmax,ss	1	N	15	15	3	4	2	2	3
		Mean	1.686	2.023	3.02	6.06	4.58	4.45	5.37
		SD	0.62	0.8251	0.53	0.79	0.88	0.07	1.79
	4	N	10	12		3	2		2
		Mean	2.554	3.066		9.63	11.07		8.22
		SD	0.4775	0.8658		2.79	1.74		2.48
	6	N				1			
		Mean				7.14			
		SD				.			
Cmin,ss	1	N	15	15	3	4	2	2	3
		Mean	0.41	0.375	0.48	0.73	0.74	1.05	1.25
		SD	0.1955	0.1001	0.09	0.24	0.48	0.16	0.42
	4	N	10	12		3	2		2
		Mean	1.18	1.263		4.45	4.13		3.35
		SD	0.2803	0.3574		0.69	0.52		0.44
	6	N				1			
		Mean				4.29			
		SD				.			

1: Cohort 4 Subutex/RBP-6000 8mg/100mg
2: Cohort 2 Subutex/RBP-6000 12mg/100mg
3: Cohort 6 Subutex/RBP-6000 8mg/300mg, 12mg/300mg, 16mg/300mg, 20mg/300mg, 24mg/300mg
SD: standard deviation

The observed arithmetic mean Cavgs buprenorphine concentrations ranged from approximately 0.62 to 0.69 ng/mL and approximately 1.45 to 2.19 ng/mL for 100 and 300 mg RBP-6000 doses, respectively, after Sublocade Injection 1.

After Sublocade Injection 4, observed steady-state arithmetic mean Cavg buprenorphine concentrations were approximately 1.89-1.9 ng/mL and approximately 4.81 ng/mL (N=2) for 100 and 300 mg RBP-6000 doses, respectively, (Table 31 and Table 32).

Comparing the observed mean buprenorphine concentrations (Cavg) between Sublocade 100 and 300 mg doses to Subutex SL 12 and 24 mg stabilization doses, buprenorphine concentration after Sublocade fourth injection were approximately 11 and 65% higher than that of Subutex 12 and 24

mg, respectively, at steady state. (1.71 vs 1.89 ng/mL and 2.91 vs 4.81 ng/mL, for Subutex vs Sublocade, respectively). After the fourth Sublocade injection the buprenorphine exposure will be solely from Sublocade injections, as the buprenorphine concentrations from Subutex stabilization phase would not influence the Sublocade bupivacaine exposure, due to 4 months of time lapse since Sublocade first injection. Thus, this comparison is scientifically justified although it is a cross treatment comparison.

Comparisons of buprenorphine Cavg,ss, C_{max},ss, and Cmin,ss, and summary overall comparison of Sublocade 100 and 300 mg and Subutex SL tablet are presented in Table 33, 34, 35, and 36 respectively.

Table 33 Buprenorphine Cavg,ss comparison between 100 and 300 mg RBP-6000 SC injections and "lead-in" Subutex SL tablet daily administration

PK parameter	Subutex SL mg	Steady-state Subutex SL mean	RBP-6000 mg	Inj. #	RBP-6000 SC mean	RBP-6000/Subutex ratio[a]
Cavg,ss	8*	1.251	100	1	0.615	0.513
				4	1.897	1.624
	12#	1.707	100	1	0.687	0.404
				4	1.893	1.114
	8^	0.837[1]	300	1	1.45[4]	1.793
	12^	1.782[2]	300	1	1.89[1]	1.043
				4	4.81[3]	2.848
	16^	1.666[3]	300	1	1.76[3]	1.124
	20^	2.754[3]	300	1	1.78[3]	0.676
	24^	2.907[1]	300	1	2.19[1]	0.726

1: N=3 2: N=4 3: N=2;
*: Cohort 4 Subutex/RBP-6000 8mg/100mg
#: Cohort 2 Subutex/RBP-6000 12mg/100mg
^: Cohort 6 Subutex/RBP-6000 8mg/300mg, 12mg/300mg, 16mg/300mg, 20mg/300mg, 24mg/300mg
a: Geometric mean ratio

Table 34 Buprenorphine Cmax,ss comparison between 100 and 300 mg RBP-6000 SC injections and "lead-in" Subutex SL tablet daily administration

PK parameter	Subutex SL mg	Steady-state Subutex SL mean	RBP-6000 mg	Inj. #	RBP-6000 SC mean	RBP-6000/Subutex ratio[a]
Cmax,ss	8*	3.964	100	1	1.686	0.447
				4	2.554	0.709
	12#	5.350	100	1	2.023	0.366
				4	3.066	0.580
	8^	2.417[1]	300	1	3.02[1]	1.332
	12^	4.77[2]	300	1	6.06[2]	1.286
				4	9.63[1]	2.003
				6	7.14[4]	1.526
	16^	4.265[3]	300	1	4.58[3]	1.141
				4	11.07[3]	2.770
	20^	10.86[3]	300	1	4.45[3]	0.429
	24^	8.267[1]	300	1	5.37[1]	0.634
				4	8.22[3]	0.991

1: N=3 2: N=4 3: N=2 4: N=1
*: Cohort 4 Subutex/RBP-6000 8mg/100mg
#: Cohort 2 Subutex/RBP-6000 12mg/100mg
^: Cohort 6 Subutex/RBP-6000 8mg/300mg, 12mg/300mg, 16mg/300mg, 20mg/300mg, 24mg/300mg
a: Geometric mean ratio

Table 35 Buprenorphine Cmin,ss comparison between 100 and 300 mg RBP-6000 SC injections and "lead-in" Subutex SL tablet daily administration

PK parameter	Subutex SL mg	Steady-state Subutex SL mean	RBP-6000 mg	Inj. #	RBP-6000 SC mean	RBP-6000/Subutex ratio[a]
Cmin,ss	8*	0.568	100	1	0.41	0.723
				4	1.18	2.218
	12#	0.806	100	1	0.375	0.505
				4	1.263	1.687
	8^	0.482[1]	300	1	0.48[1]	1.000
	12^	0.777[2]	300	1	0.73[2]	0.987
				4	4.45[3]	6.199
				6	4.29[4]	6.017
	16^	0.763[3]	300	1	0.74[3]	0.982
				4	4.13[3]	6.107
	20^	1.134[3]	300	1	1.05[3]	0.934
	24^	1.543[1]	300	1	1.25[1]	0.787
				4	3.35[3]	2.186

1: N=3 2: N=4 3: N=2 4: N=1
*: Cohort 4 Subutex/RBP-6000 8mg/100mg
#: Cohort 2 Subutex/RBP-6000 12mg/100mg
^: Cohort 6 Subutex/RBP-6000 8mg/300mg, 12mg/300mg, 16mg/300mg, 20mg/300mg, 24mg/300mg
a: Geometric mean ratio

Table 36 Summary comparison of buprenorphine mean pharmacokinetic parameters between Subutex and TRADENAME after first and fourth subcutaneous injections

Pharmacokinetic parameters	Subutex daily stabilization		RBP 6000			
Mean	12 mg	24 mg	100 mg^ (1st injection)	100 mg^ (4th injection)	300 mg# (1st injection)	300 mg# (4th injection)
$C_{avg,ss}$ (ng/ml)	1.71	2.91	0.69	1.89	2.19	4.81*
$C_{max,ss}$ (ng/ml)	5.35	8.27	2.02	3.01	5.37	9.64*
$C_{min,ss}$ (ng/ml)	0.81	1.54	0.38	1.26	1.25	4.04*

^With Subutex 12 mg stabilization
#With Subutex 24 mg stabilization
*Overall value from Cohort 6-after fourth injection the buprenorphine exposure will be solely from Sublocade injections, as the buprenorphine concentrations from Subutex stabilization phase would not influence the Sublocade bupivacaine exposure, due to 4 months of time lapse since Sublocade first injection.

3.3.9 Does Sublocade show linear pharmacokinetic behavior?

Dose Proportionality Analysis

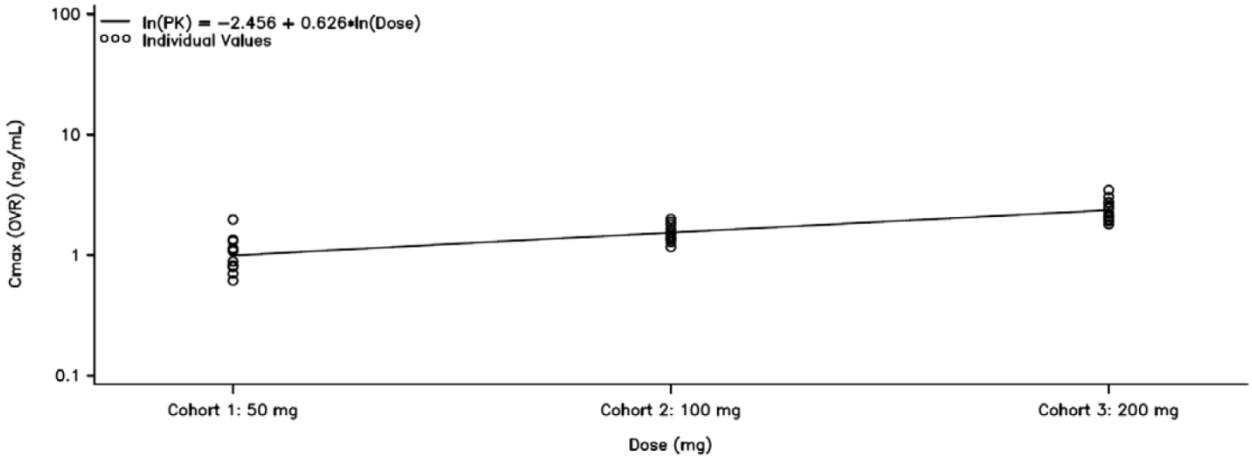
Single dose

Study RB-US-11-0020 evaluated pharmacokinetics for a single dose of 50 mg, 100 mg, 200 mg RBP-6000 SC injection (Cohorts 1, 2, and 3, respectively), and for a single dose of 100 mg RBP-6000 SC injection following a 7-day buprenorphine sublingual stabilization or "lead-in" phase to achieve a stable buprenorphine dose of 12 mg/day in subjects with opioid use disorder (Cohort 4).

Statistical analyses were done using a power model (Smith, 2000) with mixed effects of the following general form, $\ln(PK) = \ln(\beta 0) + \beta 1 \cdot \ln(Dose) + \varepsilon$, where, PK is the pharmacokinetic parameter tested (e.g., Cmax or AUC), $\ln(\beta 0)$ is the y-intercept, $\beta 1$ is the slope (a value of $\beta 1 \approx 1$ indicates linearity), and ε is an error term. The estimate of $\beta 1$ was reported along with the associated p-value and the dose range for proportionality. A significant difference from unity (1.0000) and lack of proportionality was defined a priori as $p < 0.05$.

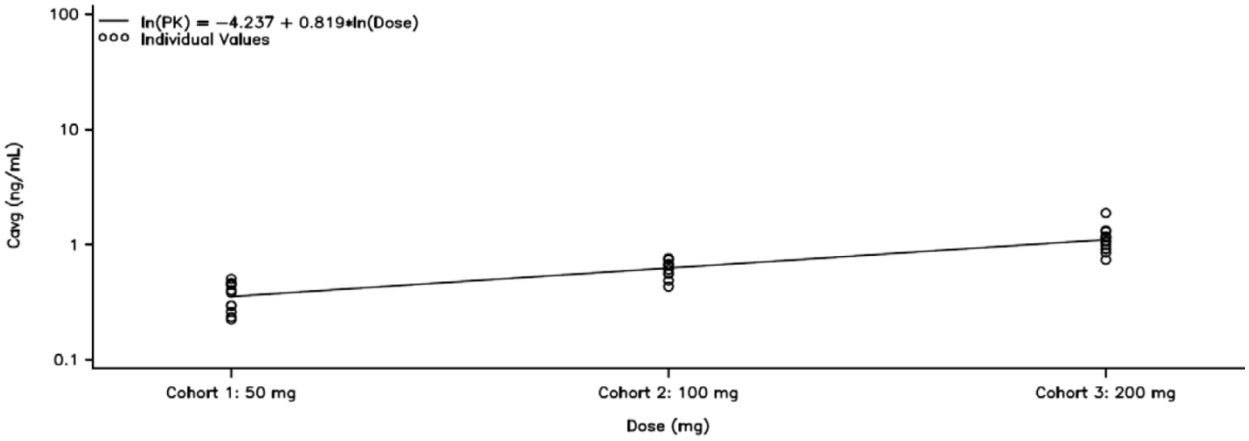
Plots of buprenorphine PK parameters versus dose are presented in Figure 35, Figure 36, and Figure 37, for overall Cmax, Cavg, and AUC1-29D, respectively.

Figure 35 Plot of Buprenorphine Overall C_{max} versus Dose on a Logarithmic Scale



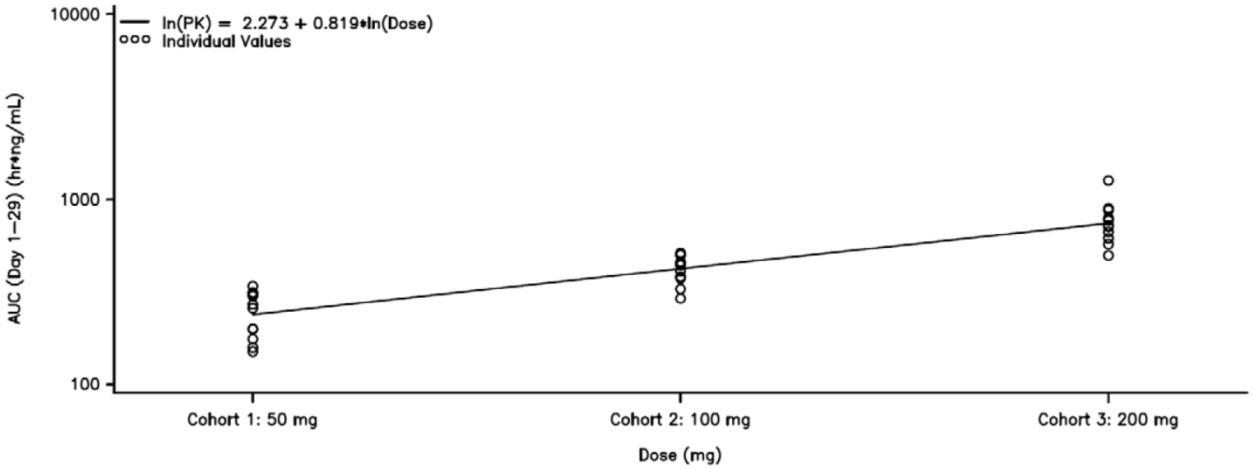
Cohort 1 = a single SC injection of RBP-6000 containing 50 mg buprenorphine.
Cohort 2 = a single SC injection of RBP-6000 containing 100 mg buprenorphine.
Cohort 3 = a single SC injection of RBP-6000 containing 200 mg buprenorphine.
Source: Figure 14.2.11.1and Table 14.2.1.5

Figure 36 Plot of Buprenorphine Overall C_{avg} versus Dose on a Logarithmic Scale



Cohort 1 = a single SC injection of RBP-6000 containing 50 mg buprenorphine.
Cohort 2 = a single SC injection of RBP-6000 containing 100 mg buprenorphine.
Cohort 3 = a single SC injection of RBP-6000 containing 200 mg buprenorphine.
Source: Figure 14.2.11.1and Table 14.2.1.5

Figure 37 Plot of Buprenorphine Overall $AUC_{Day\ 1\text{-}29}$ versus Dose on a Logarithmic Scale



Cohort 1 = a single SC injection of RBP-6000 containing 50 mg buprenorphine.
Cohort 2 = a single SC injection of RBP-6000 containing 100 mg buprenorphine.
Cohort 3 = a single SC injection of RBP-6000 containing 200 mg buprenorphine.
Source: Figure 14.2.11.1and Table 14.2.1.5

The statistical analyses for dose proportionality for Cohorts 1-3 for buprenorphine are presented in Tables 37 and 38.

Table 37 Statistical analysis of dose linearity for buprenorphine from a single dose RBP-6000 50, 100 and 200 mg in Study RB-US-11-0020 (note: Cohort 2: 100 mg)

PK Parameter	**Estimate (beta1)**	**p-value**	**90% CI of Slope**
C_{max} (ng/mL)	0.626	<.001	(0.509, 0.744)
C_{avg} (ng/mL)	0.819	0.014	(0.700, 0.937)
$AUC_{Day\ 1\text{-}29}$ (h*ng/mL)	0.819	0.014	(0.700, 0.937)

CI = confidence interval; h = hour(s); PK = pharmacokinetic
Source: Table 14.2.1.5, Listing 16.2.6.2.1, Listing 16.2.6.2.2, and Listing 16.2.6.2.3

Table 38 Additional analysis comparing ratios of Cavg, Cmax and AUC0-29D

	Dose			x-fold ratio		
	50 mg	100 mg	200 mg	50 mg 1x	100 mg 2x	200 mg 4x
Cmax (ng/mL)	1.05	1.54	2.43	1.00	1.46	2.31
Cavg (ng/mL)	0.37	0.63	1.14	1.00	1.71	3.08
AUCDay1-29 (hr ng/mL)	248.48	425.13	764.92	1.00	1.71	3.08

With the increase in dose from 50 mg to 200 mg, buprenorphine overall AUCDay1-29, Cmax, and Cavg increased at a rate that was less than proportional to dose, as depicted by the associated slope values being less than unity. The difference from unity was statistically significant for all of the above parameters in the initial burst period, secondary peak period, and entire profile (slope [$\beta 1$] = 0.819, $p = 0.014$ for AUCDay1-29; $\beta 1 = 0.626$, $p < 0.001$ for Cmax; and $\beta 1 = 0.819$, $p = 0.014$ for overall Cavg).

Multiple dose

Study RB-US-12-0005 was an open-label, multicenter study which evaluated pharmacokinetics of multiple dose Sublocade injections in adult subjects seeking treatment for opioid dependence previously on buprenorphine SL treatment. Subjects were stabilized over a 13-day period on various doses of Subutex SL tablets followed by 50, 100, 200 mg or 300 mg Sublocade multiple dose injections (Table x).

Statistical analyses were done using a power model (Smith, 2000) with mixed effects of the following general form, $\ln(PK) = \ln(\beta 0) + \beta 1 \cdot \ln(Dose) + \varepsilon$, where, PK is the pharmacokinetic parameter tested (e.g., Cmax or AUC), $\ln(\beta 0)$ is the y-intercept, $\beta 1$ is the slope (a value of $\beta 1 \approx 1$ indicates linearity), and ε is an error term. The estimate of $\beta 1$ was reported along with the associated p-value and the dose range for proportionality. A significant difference from unity (1.0000) and lack of proportionality was defined a priori as $p < 0.05$. Additionally, dose proportionality was declared if the 90% CI for beta1 was entirely within the critical region.

Table 39 displays buprenorphine Cmax and AUCtau parameters for individual cohorts, 1-5 and 6.

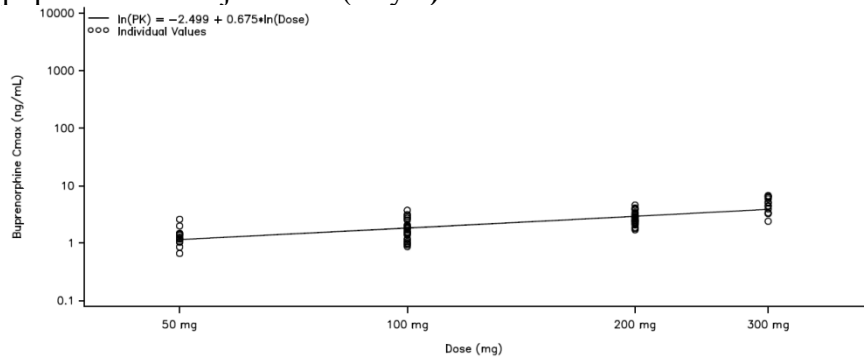
Table 39 Mean buprenorphine pharmacokinetic parameters for individual cohorts from Injections 1, and 4.

	Cohort									
	1	4	2	5	3	6				
Subutex mg	8	8	12	14	24	8	12	16	20	24
Sublocade mg	50	100	100	200	200	300				
Injection 1 - Day1										
AUCtau	246.65	413.44	461.37	756.05	642.01	970.86	1269.19	1181.34	1193.31	1473.47
Cmax	1.35	1.69	2.02	2.86	2.73	3.02	6.06	4.58[2]	4.45[2]	5.37
Injection 4 - Day 85										
AUCtau	667.61	1275.10	1272.05	2051.99	1932.07			3230.87[2]		
Cmax	2.09	2.55	3.07	4.40	4.53		9.63	11.07		8.22
	4 Sublocade injections at 28-day intervals					Up to 6 Sublocade injections at 28-day intervals				

1: N=1; 2: N=2; 3: N=3; Subutex and Sublocade in mg doses; AUC0-24: ng h/mL; AUCtau("28day"): ng h/mL; Cavg: ng/mL; Cmax: ng/mL; Cmin: ng/mL

Buprenorphine PK parameters versus dose from all cohorts are presented in Figure 38, Figure 39, Figure 40, and Figure 41, for overall Cmax, and AUCtau("28day"), respectively, for Day 1 and 4, respectively.

Figure 38 Plot linear regression of buprenorphine Cmax vs. dose on a logarithmic scale: overall population PK Injection 1 (Day 1**)** dose



Reference: Table 14.2.1.4 and Listing 16.2.6.2.4
Program: F_REGR.SAS Version: 12AUG14 13:37

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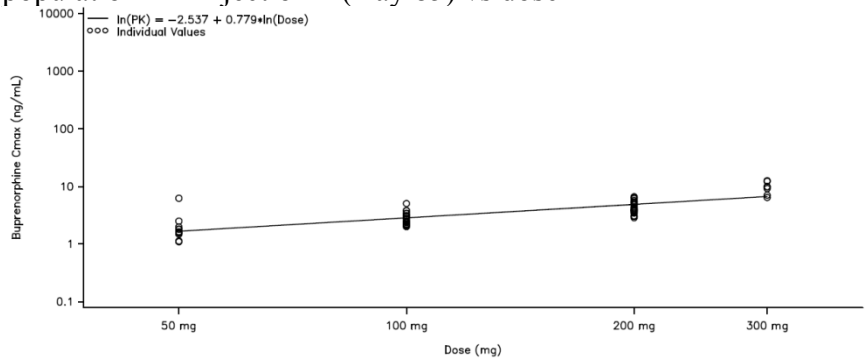
Figure 39 Plot linear regression of buprenorphine Cmax vs. dose on a logarithmic scale: overall population PK Injection 4 (Day 85) vs dose



Reference: Table 14.2.1.4 and Listing 16.2.6.2.4
Program: F_REGR.SAS Version: 12AUG14 13:37

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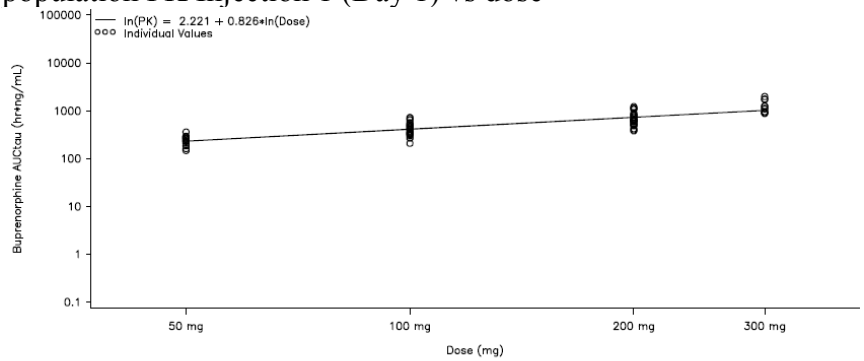
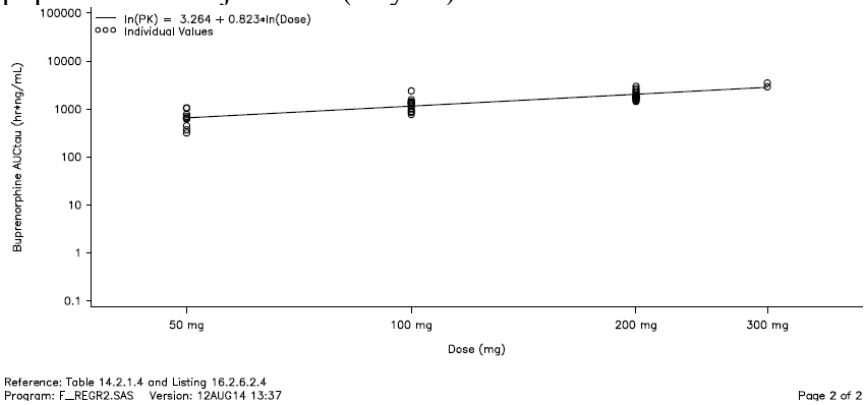
Figure 40 Plot linear regression of buprenorphine AUCtau vs. dose on a logarithmic scale: overall population PK Injection 1 (Day 1) vs dose



Reference: Table 14.2.1.4 and Listing 16.2.6.2.4
Program: F_REGR2.SAS Version: 12AUG14 13:37

Page 1 of 2

Figure 41 Plot linear regression of buprenorphine AUCtau vs. dose on a logarithmic scale: overall population PK Injection 4 (Day 85) vs dose



With the increase in dose from 50 mg to 300 mg following RBP-6000 Injection 1, and 4, the overall mean (geometric) Cmax and AUCtau for buprenorphine increased at a rate that was not proportional to dose. As the associated 90% CI of the slope was not entirely contained in the critical region, the increase in buprenorphine concentration is considered less than dose proportional.

The statistical analyses for dose proportionality for Cohorts 1-3 for buprenorphine are presented in Table 40.

Table 40 Statistical analysis of dose linearity for buprenorphine from a multiple dose Sublocade 50 to 300 mg in Study RB-US-12-0005

PK	Injection	Estimate	p-value	90% CI of Slope	Critical Region
C_{max}	1	0.675	<0.001	(0.573, 0.776)	(0.875, 1.125)
	4	0.779	0.003	(0.659, 0.898)	(0.875, 1.125)
AUCtau	1	0.826	0.003	(0.731, 0.922)	(0.875, 1.125)
	4	0.823	0.023	(0.697, 0.950)	(0.875, 1.125)

3.3.10 What are alternative dosing regimen and/or management strategy required for subpopulations?

Hepatic and renal impairment

No dedicated RBP-6000 pharmacokinetic studies were conducted in hepatically-impaired or renally-impaired patients.

With respect to hepatic impairment, the effect on buprenorphine PK has been previously evaluated with Suboxone sublingual tablets (2 mg/0.5 mg buprenorphine/naloxone) in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria (see Suboxone Film Prescribing Information 2017). The labeling states that "While no clinically relevant changes were observed

in subjects with mild hepatic impairment, buprenorphine plasma exposure was increased by 64% and 181% in subjects with moderate and severe hepatic impairment, respectively, compared to healthy subjects." Due to the lack of first-pass effect, the effect of hepatic impairment on pharmacokinetics of RBP-6000 is expected to be less than the effect on Suboxone sublingual film.

With respect to renal impairment, the information provided with Suboxone sublingual film was referenced (no differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine), indicating that buprenorphine undergoes hepatic extraction and metabolism and that buprenorphine systemic clearance is not significantly related to renal function.

Geriatric

No dedicated RBP-6000 pharmacokinetic studies were conducted in elderly patients. It is generally accepted that reported clinical experience with buprenorphine has not identified differences in responses between elderly and younger patients. Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in geriatric patients, the decision to should be made cautiously in individuals 65 years of age or older and these patients should be monitored for signs and symptoms of toxicity or overdose (Noted from Subutex Label).

3.3.11 Are there any potential drug interactions for Sublocade with other drugs?

No dedicated RBP-6000 pharmacokinetic studies were conducted to evaluate drug interactions. Buprenorphine is mainly metabolized via CYP3A4; co-administration of other drugs which are inhibitors or inducers of CYP3A4 activity can affect the pharmacokinetics of RBP-6000. Due to the lack of first-pass effects for RBP-6000, the magnitude of drug interaction with a 3A4 inhibitor or inducer is expected to be less for RBP-6000 in comparison to SL buprenorphine products (See Section 3.3 for discussion). With SL administration, a portion of the dose is typically swallowed.

Although dedicated drug-interaction studies were not conducted, the effects of co-administered inducers or inhibitors have been established in studies using transmucosal buprenorphine and the effects may be dependent on the route of administration. Since it may not be possible to consider dose adjustment in patients who are on CYP3A4 inhibitors/inducers, the following steps may be necessary and considered for Sublocade.

Patients who transfer to Sublocade treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inhibitors should be monitored to ensure that the plasma buprenorphine level provided by Sublocade is adequate. If patients already on Sublocade require newly-initiated treatment with CYP3A4 inhibitors, the patients should be monitored for signs and symptoms of over- medication. Within 2 weeks of Sublocade administration (due to possibility of remove Sublocade surgically), if the concomitant medication cannot be reduced or discontinued, it may be necessary to remove the Sublocade and treat the patient with a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilized on Sublocade in the setting of concomitant medication that is a CYP3A4 inhibitor, and the concomitant medication is discontinued, the patient should be monitored for withdrawal. If the

dose of Sublocade is not adequate in the absence of the concomitant medication, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments.

CYP3A4 inducers may induce the metabolism of buprenorphine and, therefore, may cause increased clearance of the drug which could lead to a decrease in buprenorphine plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome. It is not known whether the effects of CYP3A4 inducers are dependent on the route of administration of buprenorphine. Patients who transfer to Sublocade treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inducers should be monitored to ensure that the plasma buprenorphine level provided by Sublocade is not excessive. If patients already on Sublocade require newly-initiated treatment with CYP3A4 inducers, the patients should be monitored for withdrawal. If the dose of Sublocade is not adequate in the absence of the concomitant medication, and the concomitant medication cannot be reduced or discontinued, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilized on Sublocade in the setting of concomitant medication that is a CYP3A4 inducer, and the concomitant medication is discontinued, the patient should be monitored for signs and symptoms of over-medication. Within 2 weeks of Sublocade administration (due to possibility of remove Sublocade surgically), if the dose provided by Sublocade is excessive in the absence of the concomitant inducer, it may be necessary to remove the Sublocade and treat the patient with a formulation of buprenorphine that permits dose adjustments.

3.3.12 Describe norbuprenorphine pharmacokinetic information for Sublocade

As a SC depot administration, Sublocade avoids the first-pass effect compared to buprenorphine formulations for oral transmucosal administration. The fraction absorbed sublingually of a sublingual buprenorphine product (e.g., Suboxone) also avoids the first-pass effect, whereas the swallowed fraction still undergoes first-pass effect and is metabolized to norbuprenorphine, which will result in a higher exposure ratio of norbuprenorphine to buprenorphine.

Buprenorphine and norbuprenorphine concentrations were measured for both RBP-6000 SC and sublingual Subutex administrations in Study RB-US-11-0005, a multiple dose study. The norbuprenorphine to buprenorphine ratio was much higher for Subutex sublingual lead-in phase compared to RBP-6000 SC 300 mg after the fourth injection. The AUCtau ratio of norbuprenorphine to buprenorphine approximately ranges from 0.23 to 0.39 for RBP-6000 after the fourth injection compared to 1.32 to 3.21 for Subutex sublingual at steady state (RB-US-12-0005). This observation confirms that RBP-6000 undergoes lesser metabolism compared to buprenorphine sublingual product due to lack of first-pass effect.

Study RB-US-11-0020 results showed norbuprenorphine to buprenorphine ratios similar to that of Study RB-US-11-005. As noted previously Study RB-US-11-0020 evaluated a single dose of 50 mg, 100 mg, 200 mg RBP-6000 SC injection (Cohorts 1, 2, and 3, respectively), and for a single dose of 100 mg RBP-6000 SC injection following a 7-day buprenorphine sublingual stabilization or “lead-in” phase to achieve a stable buprenorphine dose of 12 mg/day in subjects with opioid use

disorder (Cohort 4). A summary of norbuprenorphine plasma PK parameters is presented in Table 41 for all cohorts.

Table 41 Overall norbuprenorphine pharmacokinetic parameters from a single dose RBP-6000 50, 100 and 200 mg in Study RB-US-11-0020 (note: Cohort 2: 100 mg)

			RBP-6000			RBP-6000 + SUBOXONE SL
Phase	**Parameter**	**Statistic**	**Cohort 1 50 mg**	**Cohort 2 100 mg**	**Cohort 3 200 mg**	**Cohort 4 100 mg**
Overall	$AUC_{Day\ 1\text{-}29}$ (hr*ng/mL)	n	12	12	12	11
		Mean	87.173	130.410	234.712	424.299
		%CV	54.0	39.1	32.0	48.1
		Median	76.564	126.337	255.369	380.904
		Min,Max	33.29, 176.81	62.94, 208.71	117.30, 360.37	127.97, 852.77
		Geometric Mean	76.759	121.285	222.670	379.273
	C_{avg} (ng/mL)	n	12	12	12	11
		Mean	0.130	0.194	0.349	0.631
		%CV	54.0	39.1	32.0	48.1
		Median	0.114	0.188	0.380	0.567
		Min,Max	0.05, 0.26	0.09, 0.31	0.17, 0.54	0.19, 1.27
		Geometric Mean	0.114	0.180	0.331	0.564
	C_{max} (ng/mL)	n	12	12	12	12
		Mean	0.258	0.381	0.695	2.755
		%CV	60.3	50.4	40.2	42.5
		Median	0.203	0.373	0.685	2.605
		Min,Max	0.10, 0.62	0.17, 0.71	0.30, 1.22	1.24, 4.95
		Geometric Mean	0.222	0.336	0.640	2.528
	C_{min} (ng/mL)	n	12	12	12	12
		Mean	0.028	0.025	0.052	0.074
		%CV	34.3	25.2	51.9	104.8
		Median	0.027	0.022	0.043	0.043
		Min,Max	0.02, 0.06	0.02, 0.04	0.03, 0.11	0.02, 0.29
		Geometric Mean	0.027	0.024	0.046	0.053
	t_{max} (hr)	n	12	12	12	12
		Median	204.000	468.092	264.025	5.000
		Min,Max	48.00, 3581.02	48.00, 1825.80	4.00, 1130.60	2.00, 48.00
	$t_{½}$ (hr)	n	4	7	6	7
		Mean	1509.809	980.190	1155.986	847.074
		SD	743.6310	515.1271	162.7057	582.0241
		%CV	49.3	52.6	14.1	68.7
		Median	1330.440	851.461	1118.972	595.519
		Min,Max	858.39, 2519.96	363.30, 1776.99	918.02, 1355.54	66.79, 1694.39
		Geometric Mean	1383.795	856.743	1146.284	603.364
	$R_{AUClast}$	n	12	12	12	12
		Mean	0.295	0.270	0.243	0.517
		%CV	48.0	54.1	36.6	97.6
		Median	0.295	0.240	0.214	0.391
		Min,Max	0.11, 0.58	0.12, 0.62	0.17, 0.49	0.15, 2.09
		Geometric Mean	0.265	0.241	0.232	0.413
	R_{Cmax}	n	12	12	12	12
		Mean	0.220	0.223	0.260	1.084
		%CV	50.3	54.8	42.3	43.4
		Median	0.202	0.193	0.258	0.960
		Min,Max	0.09, 0.42	0.09,0.48	0.12, 0.44	0.50, 2.16
		Geometric Mean	0.197	0.196	0.238	1.004

%CV = coefficient of variation; hr = hour; Max = maximum; Min = minimum; PK = pharmacokinetic; QD = once daily; SC = subcutaneous;
SD = standard deviation; SL = sublingual
Cohort 1 = a single SC injection of RBP-6000 containing 50 mg buprenorphine.
Cohort 2 = a single SC injection of RBP-6000 containing 100 mg buprenorphine.
Cohort 3 = a single SC injection of RBP-6000 containing 200 mg buprenorphine.

Cohort 4 = QD dosing with SUBOXONE SL, 8 mg (two 4 mg doses approximately 3 hours apart) on Day -7 and 12 mg on Days -6 through -1.
Source: Table 14.2.1.3, Listing 16.2.6.2.1, Listing 16.2.6.2.2, and Listing 16.2.6.2.3
AUClast Area under the plasma concentration-time curves from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
RAUClast: Ratio of AUClast norbuprenorphine/AUClast buprenorphine (concentration was converted to molar concentration);
RCmax: Ratio of Cmax norbuprenorphine/Cmax buprenorphine (Cmax was converted to molar concentration; buprenorphine molecular weight [MW]: 467.64, norbuprenorphine MW: 413.55)

Like buprenorphine, norbuprenorphine exposure parameters increased with increasing dose of RBP-6000 from 50 mg to 200 mg. However, Cohort 4 showed much greater norbuprenorphine exposure compared to Cohort 2 (100 mg RBP-6000) and Cohort 3 (200 mg RBP-6000). Norbuprenorphine AUCDay1-29 (geometric mean) for Cohort 4 was greater by 3.1-fold and 1.7-fold compared to Cohort 2 and Cohort 3, respectively. Norbuprenorphine Cmax (geometric mean) for Cohort 4 was 7.5-fold and 4-fold greater compared to Cohort 2 and Cohort 3, respectively. Similar to findings in Study RB-US-11-0005, metabolite to parent (norbuprenorphine/buprenorphine) ratios ranged from 0.232 to 0.413 for all Cohorts. It was noted that the ratio from Cohort 2 was lower compared to Cohort 4 (0.241 and 0.413, respectively).

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Pharmacokinetic (PK) samples were analyzed using validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methods for buprenorphine and norbuprenorphine in human plasma. The following buprenorphine and norbuprenorphine concentration ranges were used in Study 11-0020: Buprenorphine: 0.0250-5.00 ng/mL; Norbuprenorphine: 0.0200-4.00 ng/mL, respectively (lower limit of detection (LLOQ): 0.025 and 0.02 ng/mL for buprenorphine and norbuprenorphine, respectively). The following buprenorphine and norbuprenorphine concentration ranges were used in Studies 12-0005, 13-0002, 13-0001, 13-0006: Buprenorphine: 0.0500-25.0 ng/mL; Norbuprenorphine: 0.0400-20.0 ng/mL, respectively (LLOQ: 0.05 and 0.04 ng/mL for buprenorphine and norbuprenorphine, respectively). Typical percent values for QC intraday precision and accuracy ranged from 0.7 to 5.0 and -9.0 to -2.0, respectively. Typical percent values for QC inter-day precision and accuracy ranged from 2.2 to 4.2 and -7.0 to -3.3, respectively. Quality control (QC) samples for buprenorphine and norbuprenorphine analyzed on the given specific analyses days were 0.075, 0.5, 4 ng/mL and 0.06, 0.4, 3.2 ng/mL, respectively, for Study 11-0020. Percent CV observed ranged from 4 to 6.4 and 3.5 to 8.1 for buprenorphine and norbuprenorphine, respectively. Quality control (QC) samples for buprenorphine and norbuprenorphine analyzed on the given specific analyses days were 0.15, 2, 20 ng/mL and 0.12, 1.6, 16 ng/mL, respectively, for Studies 12-0005, 13-0002, 13-0001, 13-0006. Typical percent CV observed ranged from 4.3 to 10.1 and 1.8 to 10.5 for buprenorphine and norbuprenorphine, respectively. The analytical information provided by the Applicant is acceptable and there are no further information needed regarding bioanalytical information.

4.2 Population PK Analyses

4.2.1 M04 – PPK of 12-0005 and 13-0001:

Report M04 is titled "*RBP-6000: POPULATION PHARMACOKINETIC/PHARMACODYNAMIC MODELING ANALYSES Population Pharmacokinetic and Exposure-Response Analyses for Buprenorphine after Repeated Subcutaneous Injections of RBP-6000 in Treatment-Seeking Subjects with Opioid Use Disorder*".

Applicant conducted population pharmacokinetic and exposure-response analyses for buprenorphine following repeat sub-cutaneous injections of RBP-6000 in treatment-seeking subjects with opioid use disorder. The purpose of these analyses is to provide evidence-based support for dosing regimens and identify potential dose adjustments for specific patient subpopulations in order to achieve the intended target therapeutic effect.
This section will include the population PK analyses. The PKPD and exposure-response analyses can be found in section 4.3 of this review.

Data from the following clinical studies were included in the analyses:

- **RB-US-12-0005 (Phase 2a)**: An Open-Label, Multicenter, Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics, Efficacy Markers, and Opioid Receptor Availability of Subcutaneous Injections of Depot Buprenorphine (RBP-6000) in Treatment Seeking Opioid-Dependent Subjects
    - **Rich and Sparse PK** – Subutex SL Tablets: pre-dose on Day -7 to Day -1, then at 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose on Day -1
    - **Rich PK** – RBP-6000:
        - Injection 1: pre- injection (corresponding to 24 hours post-dose for SUBUTEX on Day -1), 1, 2, 4, 6, 8, 12, 20, 24, 25, 26, 28, 30, 32, 36, 44 and 48 hours post-injection, and days 6, 8, 10, 13, 16, 19, 22 and 25 post-injection
        - Injections 2 and 3: pre- injection, 1, 12 and 24 hours post-injection, and days 2, 8, 13, and 19 post-injection
        - Injection 4:
            - 50-200 mg: pre-injection, 1, 2, 4, 6, 8, 12, 20, 24, 25, 26, 28, 30, 32, 36, 44, and 48 hours post-injection, and days 6, 8, 10, 13, 16, 19, 22, 25, 28, 36, 42, 50 and 56 days post-injection
            - 300 mg: pre-injection, 1, 2, 4, 6, 8, 12, 20, 24, 25, 26, 28, 30, 32, 36, 44, and 48 hours post-injection, and days 6, 8, 10, 13, 16, 19, 22 and 25 days post-injection
        - Injection 5: pre-injection, 1, 12 and 24 hours post-injection, and days 2, 8, 13, and 19 post-injection
        - Injection 6: pre- injection, 1, 2, 4, 6, 8, 12, 20, 24, 25, 26, 28, 30, 32, 36, 44, and 48 hours post-injection and days 6, 8, 10, 13, 16, 19, 22, 25, 28, 36, 42, 50 and 56 post-injection

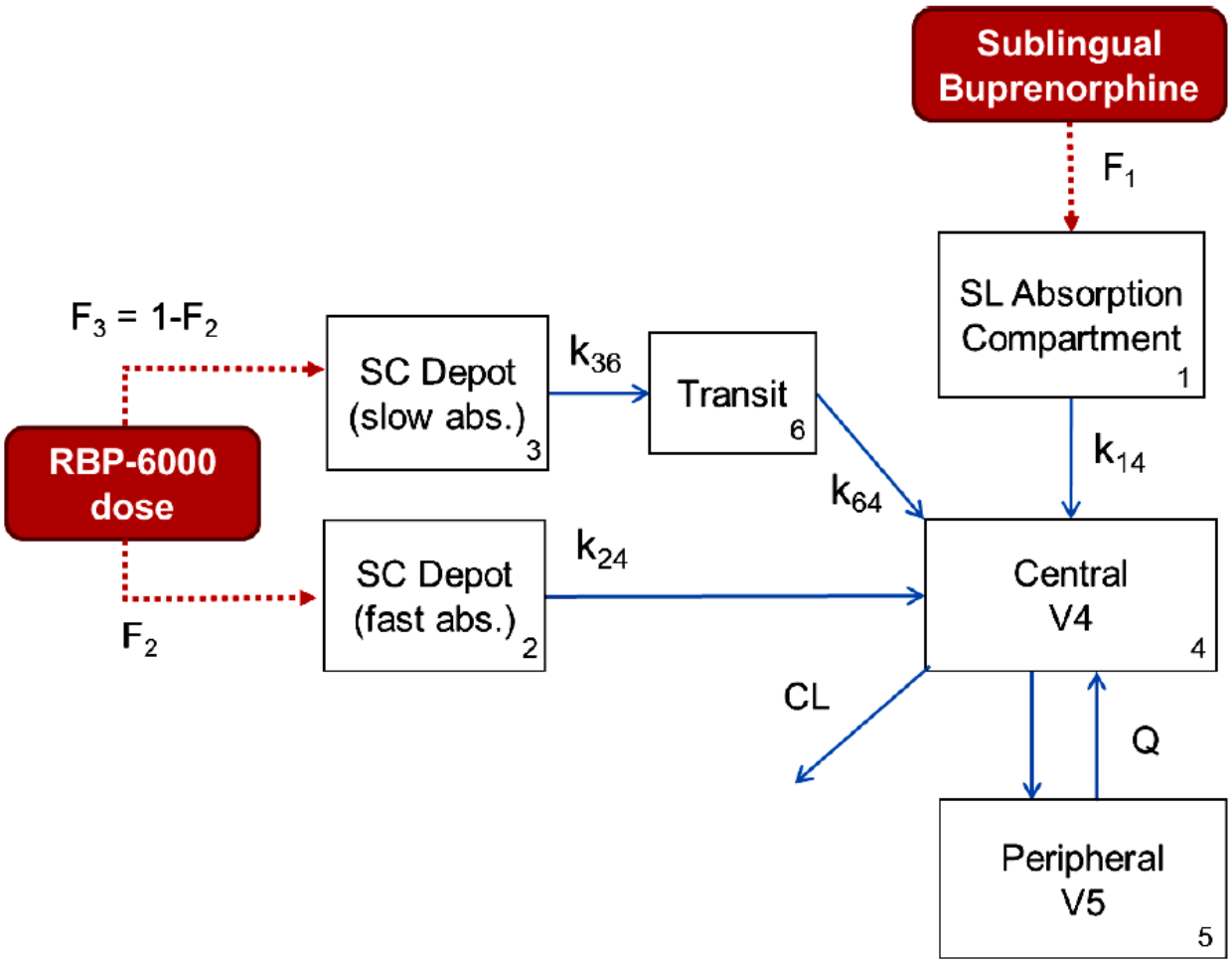
- **RB-US-13-0001 (Phase 3)**: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study To Assess the Efficacy, Safety, and Tolerability of Multiple Subcutaneous Injections of Depot Buprenorphine (RBP-6000 [100 mg and 300 mg]) Over 24 Weeks in Treatment-Seeking Subjects with Opioid Use Disorder
    - **Sparse PK** – Subutex SL Tablets: Run-in phase on Day -1 (within 1 hour prior and 1-2 hour post the SL dose), double-blind treatment phase on Days 1, 2, 8, 15, 22, 29, 30, 36, 43, 50, 57, 58, 64, 71, 78, 85, 86, 92, 99, 106, 113, 114, 120, 127, 134, 141, 142, 148, 155, 162 and 169.
    - **Rich PK** – RBP-6000 SC Injection: On Days -1, 1, 2, 8, 15, 22, 29, 30, 36, 43, 50, 57, 58, 64, 71, 78, 85, 86, 92, 99, 106, 113, 114, 120, 127, 134, 141, 142, 148, 155, 162 and 169. On days where RBP-6000 was injected (Days 29, 57, 85, 113, and 141) blood samples were taken within 1 hour prior to and at 4 hours (±15 minutes) after SC injection.

Population PK Model (m04)

The population PK model included components that were unique to Subutex SL, unique to RBP-6000, and components that were common between the two products. The Subutex SL product utilized a 2-compartment disposition model with first-order absorption. The RBP-6000 product-specific model terms included dual first-order absorption components (fast or slow absorption). The slow absorption pathway was characterized using a transit compartment.

Structural Model: The additional disposition processes were common between Subutex SL and RBP-6000 in order to properly address the flip-flop phenomenon resulting from the slow release of buprenorphine from the SC depot. This includes a central compartment, a peripheral compartment, and first-order elimination from the central compartment. The model schematic is presented in the figure below.

Figure 41: Structural model of PK data acquired for studies 12-0005 and 13-0001 following SL and SC buprenorphine administration



Source: indv-6000-m04.pdf (sequence 0001), page 36 of 487

The following is a description of the rate constants and overall PK parameters referred to in the figure above:

- F1, the relative bioavailability of SUBUTEX compared to RBP-6000;
- F2 and F3, the fractions of the RBP-6000 administered dose absorbed through the fast and slow pathways respectively; a logit transformation was applied to F2 to constrain individual PK parameter values to lie between 0 and 1. F3 was then calculated as 1- F2;
- k14, the first-order rate constant for SL (SUBUTEX) absorption;
- k24, the first-order rate constant for the fast absorption of RBP-6000;
- k36, the first-order absorption rate constant to the transit compartment related to the slower absorption of RBP-6000;
- k64, the first-order transfer rate constant from the transit to central compartment;
- CL, V4, V5 and Q: buprenorphine apparent elimination clearance, apparent central volume of distribution, apparent peripheral volume of distribution and apparent intercompartmental clearance.

Allometric Scaling: Clearance and volume were scaled using body weight using exponents of 0.75 for clearance and 1 for volume of distribution

Inter-Individual Variability: A full variance-covariance matrix was used to estimate the values of the IIV of the PK parameters and their corresponding covariance values
Residual Variability: Combined additive and proportional residual error model
Final Model: Covariates in the final model were BMI effect (via power model) on CL, BMI effect (via power model) on fast absorption rate constant from SC depot (K_{24}), and sex effect on slow absorption rate constant from SC depot (K_{36}).

The parameter estimates for the final model are shown in the table below.

[*Reviewer comment: Applicant indicates that there was an increase in inter-individual variability (IIV) of V5, Q, of 3-fold and 4.5-fold for K14, and 2-fold for F1 and K14 when Phase 3 Trial 13-0001 PK data were pooled with Phase 2a study 12-0005 PK data (compared to 12-0005 PK data alone). The Applicant attributes the increase in in IIV as being due to the potential inaccuracies in doses and dosing times for Suboxone during the run-in period of the Phase 3 trial. The inaccuracies in dosing time are plausible since Suboxone dosing information was not recorded throughout the dose stabilization period but only at protocol visits. Thus, Applicant concludes that the records for the dose units dispensed at each visit could not be used to accurately determine the unsupervised intake of Suboxone SL film between visits), which is reasonable.*

To address this concern, the Applicant fixed the values of both the fixed-effect (thetas) and random-effects (etas) for K14, F1, Q, and V5 to the values obtained based on Phase 2a Study 12-0005 PK data alone. This approach, according the Sponsor, is more robust than estimating separate IIV terms for each buprenorphine product.

Fixing the thetas and etas for K14, F1, Q, and V5 to the values based on the Phase 2a Study 12-0005 PK data is acceptable.]

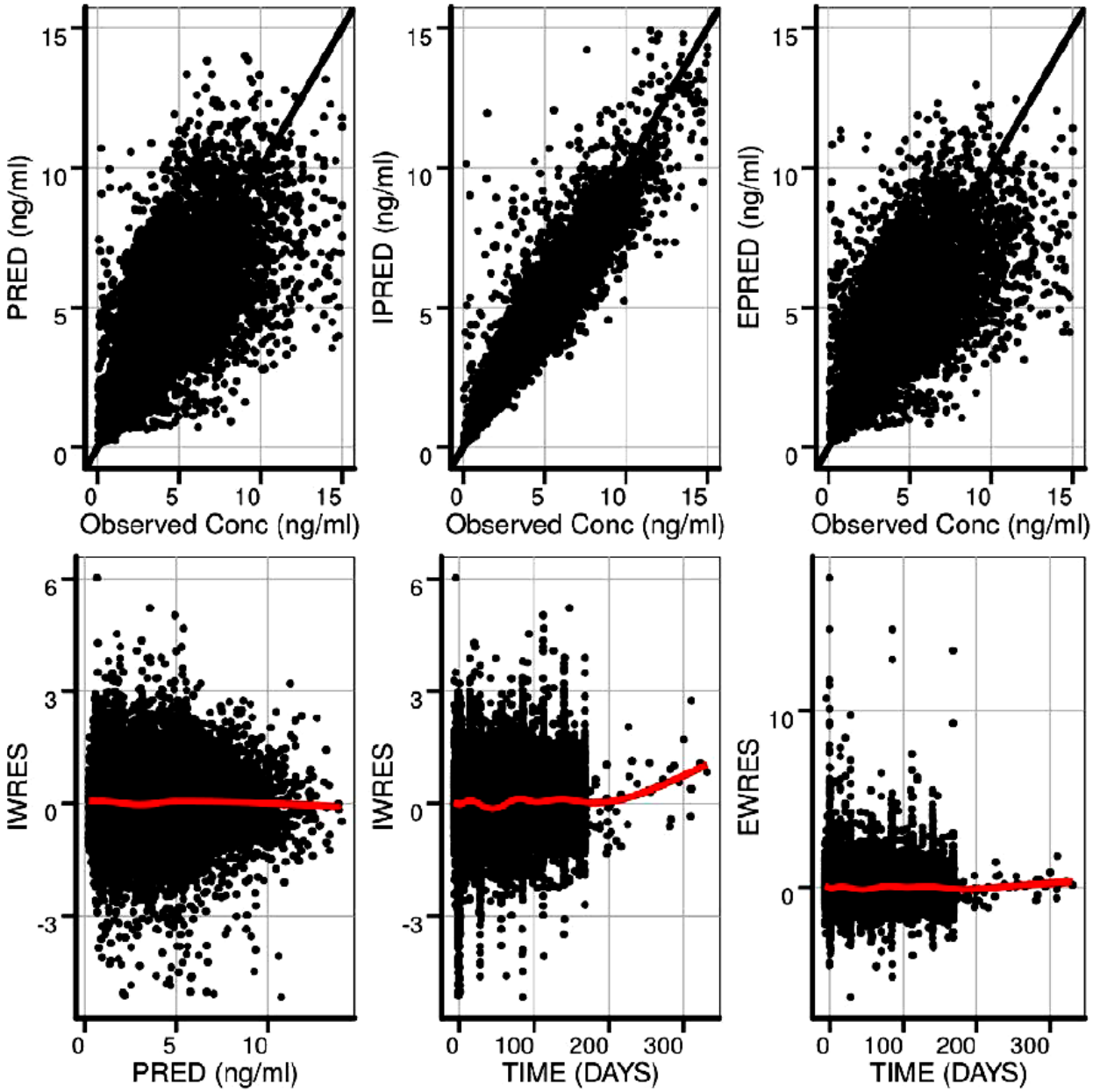
Table 41: Estimates of the Final Population Pharmacokinetic Model (run036.mod) for RBP-6000 and SL Buprenorphine Products (SUBUTEX and SUBOXONE) after Combined Analysis of Studies RBUS-12-0005 and RB-US-13-0001

PARAMETERS	DESCRIPTIONS	ESTIMATES (RSE%)	VARIANCE (RSE%)	IIV (%)
K14	Sublingual absorption rate constant (h^{-1})	1.17 (FIXED)	0.19 (FIXED)	45.7
K24	Fast absorption rate constant from SC depot ($h^{-}1$)	0.0294 (9.9)	0.758 (41)	107
K36	Slow absorption rate constant from SC depot (h^{-1})	0.0037 (8.3)	1.65 (13)	205
K64	Rate constant from Transit compartment to Central (h^{-1})	0.000483 (5.4)	0.58 (12)	88.6
CL	RBP-6000 apparent elimination clearance (L/h)	49.8 (2.8)	0.121 (16)	35.9
V4	RBP-6000 apparent volume of central compartment (L)	462 (7.4)	0.775 (40)	108
Q	RBP-6000 apparent distribution clearance (L/h)	79.5 (FIXED)	0.334 (FIXED)	62.9
V5	RBP-6000 apparent volume of peripheral compartment (L)	1110 (FIXED)	0.941 (FIXED)	125
F1	Relative bioavailability of SUBUTEX relative to RBP-6000	0.185 (FIXED)	0.195 (FIXED)	46.4
F2	Fraction of RBP-6000 dose absorbed by fast process	0.0661 (2.8)	0.223 (13)	50
ADD	Additive residual error	0.0378 (14)		
PROP	Proportional residual error	0.19 (0.97)		
FRK14	Relative change of K14 of SUBOXONE relative to SUBUTEX	0.898 (28)		
FRF1	Relative change of F1 of SUBOXONE relative to SUBUTEX	1.37 (9.1)		
F1DOSE	Relative change of F1 for dose $\geq$ 16 mg relative to dose $<$ 16mg	0.765 (36)		
$\theta_{bmi} : CL$	Power coefficient for BMI on CL	-0.408 (21)		
$\theta_{bmi} : K24$	Power coefficient for BMI on K24	-1.29 (15)		
$\theta_{female} : K36$	Fractional increase of K36 for Female relative to Male	0.0759 (140)		

Source: indv-6000-m04.pdf (sequence 0001), page 67 of 487

The diagnostic plots for the final population PK model (run036.mod) are shown in the figure below.

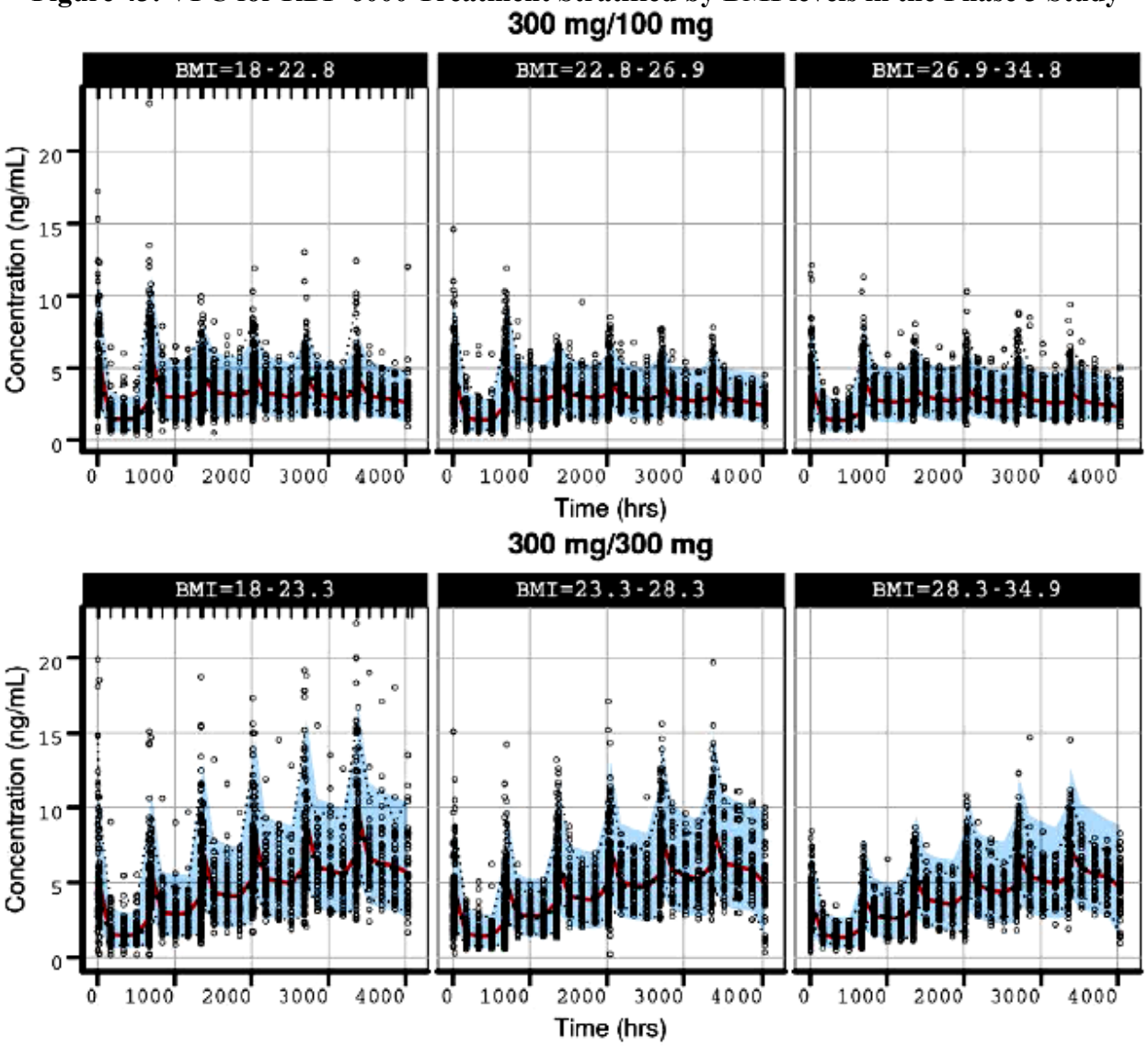
Figure 42: Diagnostic plots for the Applicant's Final Population PK Model



Source: indv-6000-m04.pdf (sequence 0001), page 122 of 487

The following plot represents the results of the Applicant's visual prediction check of the Final population PK model.

Figure 43: VPC for RBP-6000 Treatment Stratified by BMI levels in the Phase 3 Study



Source: indv-6000-m04.pdf (sequence 0001), page 68 of 487

[*Reviewer comment: The visual predictive check indicates that the model represents the data well. The diagnostic plots do not show systematic bias across the range of concentration. The IWRES versus time plot trends positive after day 200 but this is likely due to the sparse PK samples available at or after 200 days rather than a systematic bias in the model.* ***Overall, the Applicant's population PK model is acceptable****.*]

4.2.2 M05 – PPK of 12-0005, 13-0001, and 13-0003: Report M05 is titled "Population Pharmacokinetics of RBP-6000 in Treatment-Seeking Subjects with Opioid Use Disorder Combined Analysis of Studies RB-US-12-0005, RB-US-13-0001 and RB-US-13-0003".

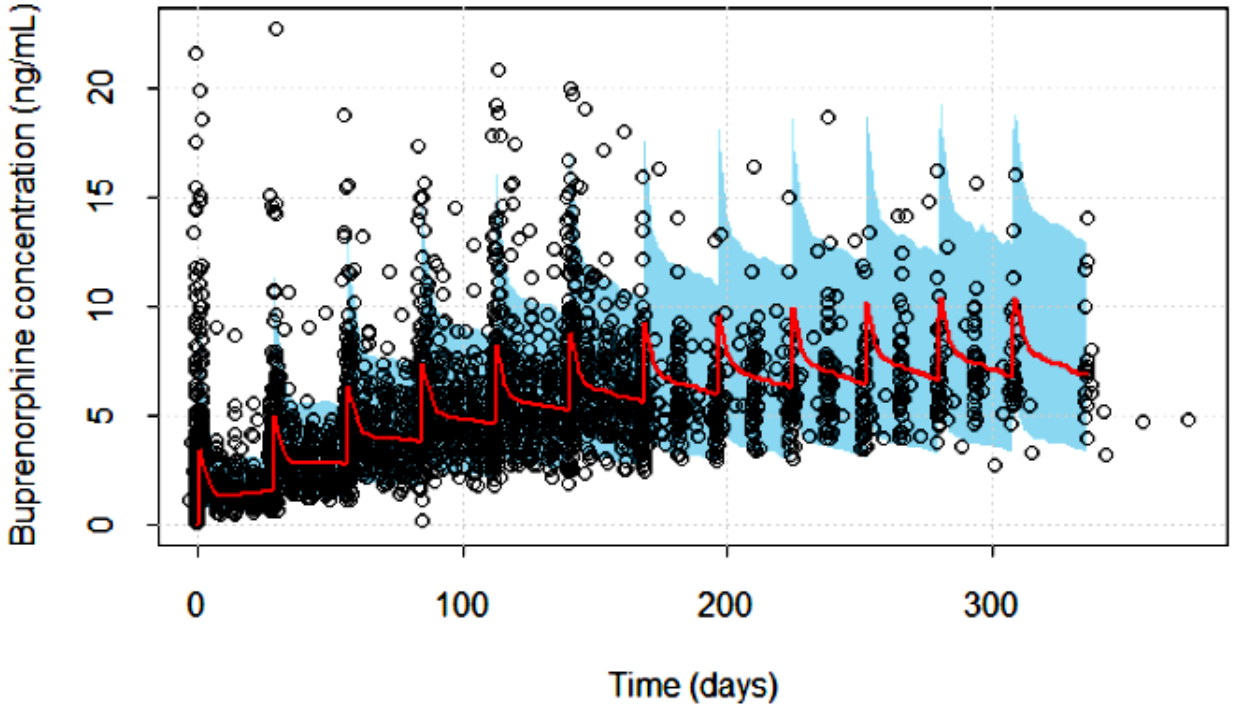
Applicant re-assessed the model generated in report M04 once the data from open-label extension study 13-0003 became available. An external validation was conducted using the study 13-0003 PK data. The model generated in m04 was used with the new data from 13-0003 to derive goodness of fit (diagnostic) plots using the previously estimated PK parameter estimates (i.e. MAXEVAL=0). Finally, the Applicant also re-estimated PK parameters for the M04 PK model by pooling the newly acquired PK data from study 13-0003 with the existing data from studies 12-0005 and 13-0001. The new PK parameter estimates for the pooled data were compared with those reported in M04.

Data for these analyses came from the following studies:

- **RB-US-12-0005 (Phase 2a), RB-US-13-0001 (Phase 3):** Information regarding studies 12-0005 and 13-0001 can be found in the section 4.2.1.
- **RB-US-13-0003 (Phase 3)**: An Open-Label, Long-Term Safety and Tolerability Study Depot Buprenorphine (RBP-6000 [100 mg and 300 mg]) in Treatment-Seeking Subjects with Opioid Use Disorder.
    - **Sparse PK** – RBP-6000 SC Injection: On Days 1, 29, 57, 85, 113 and 141, a blood sample was taken within 1 hour prior to SC injection. An additional PK sample was collected half-way into the dosing interval on days 15, 43, 71, 99, 127, and 169.

The applicant performed a visual predictive check as an external validation. The population PK model developed in report M04 was applied to simulate PK under the dose regimens administered in study 13-0003. The applicant generated 50 replicate simulations for the n=72 subjects who received 300 mg / 300 mg treatment for 6 injections in study 13-0001 and maintained at the 300 mg dose in study 13-0003 (for up to 12 injections total). Applicant retained an identical covariate configuration to those n=72 subjects receiving the 300 mg dose in trial 13-0001 and study 13-0003. The visual prediction check (VPC) plot providing a comparison of the predicted and observed PK data is shown in the Figure below.

Figure 44: VPC of Observed PK data from Patients receiving 300 mg Once monthly in 13-0001 and continued on the same dose into 13-0003 using Model Built using PK data from 13-0001 and 12-0005.



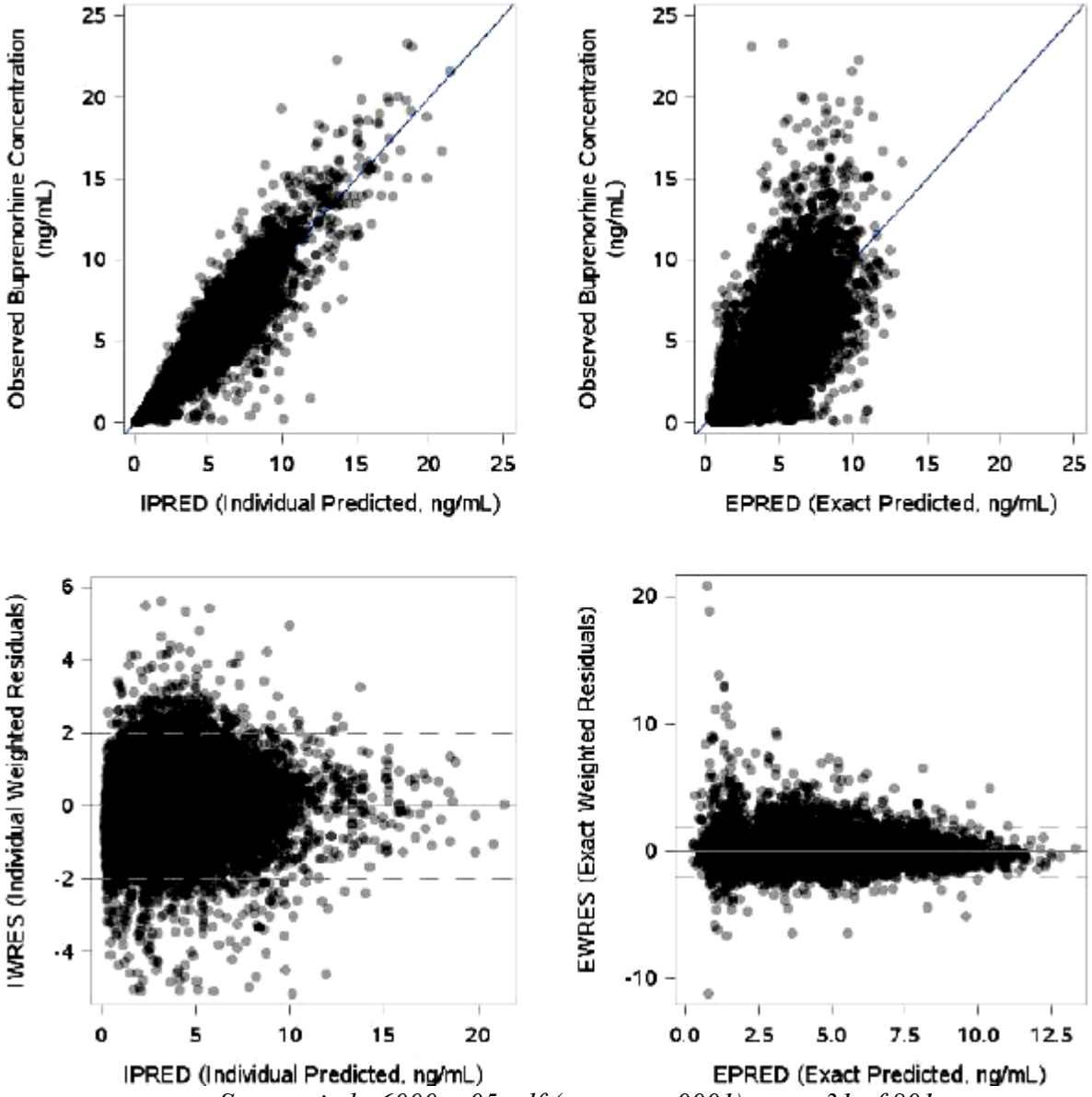
The black circles are observed data from roll-over subjects receiving 300 mg throughout both studies RB-US-13-0001 and RB-US-13-0003 (n=72); Red solid line represents the median of the simulated data; Shaded blue area represents the 90% prediction intervals of the simulated data. Simulated 13-0003 data generated using model run036 (built with 12-0005 and 13-0001 data).

Source: indv-6000-m05.pdf (sequence 0001), page 33 of 801

[*Reviewer comment: Study 13-0003 (day 180 and later) had sparse PK samples acquired every other week and thus peaks are not shown. Trial 13-0001 had rich PK sampling with sampling near T_{max} which provided capture of high concentrations (see section 4.2.1 details on PK sample collection). The visual difference in observed PK data density before versus after day 180 (when patients transitioned from 13-0001 to 13-0003) is due to the reduced frequency of PK sample acquisition (rather than a deficiency of the model). In addition, it is not expected for the PK profile to shift at or after 180 days as the dose regimen is unchanged before and after Day 180.*]

The previously developed PK model from report m04 (generated using PK data from 12-0005 and 13-0001) was used to generate diagnostic or "goodness-of-fit" plots for the newly-generated PK data from study 13-0003. The final PK parameter estimates from m04 were utilized as the initial estimates and the maximum number of evaluations was set to zero (MAXEVAL=0) to generate the residuals. The diagnostic plots for PK data from study 13-0003 using this method are displayed in the figure below.

Figure 45: Diagnostic plots of buprenorphine PK following Sublocade administration.



Source: indv-6000-m05.pdf (sequence 0001), page 31 of 801

[*Reviewer comment: The EPRED, or exact prediction as the Applicant calls it, is the population prediction (often referred to as PRED).*]

Finally, the Applicant re-estimated PK parameters for the m04 model after pooling PK data from study 13-0003 with the original dataset (12-0005 and 13-0001). The final dataset included n=792 subjects with PK data. There were 19686 PK samples with 2910 samples of Suboxone / Subutex and 16776 samples for RBP-6000. The final parameter estimates are shown in the table below.

Table 42: Comparison of PK Parameter estimates before and after adding data from study 13-0003 to studies 12-0005 and 13-0001 (Page 1 of 2)

		Studies RB-US-12-0005 and RB-US-13-0001			Studies RB-US-12-0005, RB-US-13-0001 and RB-US-13-0003		
		Population Value (θ)	Inter-Individual Variability (ω^2)		Population Value (θ)	Inter-Individual Variability (ω^2)	
Parameter	Description	Estimate (%RSE)	Estimate (%RSE)	%CV	Estimate (%RSE)	Estimate (%RSE)	%CV
CL/F (L/hr)	RBP-6000 apparent elimination clearance	49.8 (2.79)	0.121 (16.4)	35.9	52.0 (1.53)	0.0871 (9.45)	30.2
V4/F (L)	RBP-6000 apparent volume of central compartment	462 (7.45)	0.775 (39.6)	108	433 (26.7)	0.647 (12.2)	95.4
Q/F (L/hr)	RBP-6000 apparent distribution clearance	79.5 (FIXED)	0.334 (FIXED)	63.0	79.5 (FIXED)	0.334 (FIXED)	63.0
V5 (L)	RBP-6000 apparent volume of peripheral compartment	1110 (FIXED)	0.941 (FIXED)	125	1110 (FIXED)	0.941 (FIXED)	125
K14	Sublingual absorption rate constant (h-1)	1.17 (FIXED)	0.190 (FIXED)	45.7	1.17 (FIXED)	0.190 (FIXED)	45.7
K24 (1/hr)	Fast absorption rate constant from SC depot	0.0294 (9.86)	0.758 (41.0)	106	0.0276 (5.07)	0.654 (15.7)	96.1
K36 (1/hr)	Slow absorption rate constant from SC depot	0.00370 (8.30)	1.65 (12.6)	205	0.00362 (7.38)	1.54 (10.9)	191
K64 (1/hr)	Rate constant from Transit compartment to Central	0.000480 (5.42)	0.580 (12.3)	88.7	0.000510 (3.73)	0.432 (10.5)	73.5
F1	Relative bioavailability of SUBUTEX compared to RBP-6000	0.185 (FIXED)	0.195 (FIXED)	46.4	0.185 (FIXED)	0.195 (FIXED)	46.4
F2	Fraction of RBP-6000 dose absorbed by fast process	0.0661 (2.84)	0.223 (13.3)	50.0	0.0679 (2.24)	0.204 (11.2)	47.6

Source: indv-6000-m05.pdf (sequence 0001), page 35 of 801

Table 43: Comparison of PK Parameter estimates before and after adding data from study 13-0003 to studies 12-0005 and 13-0001 (Page 2 of 2)

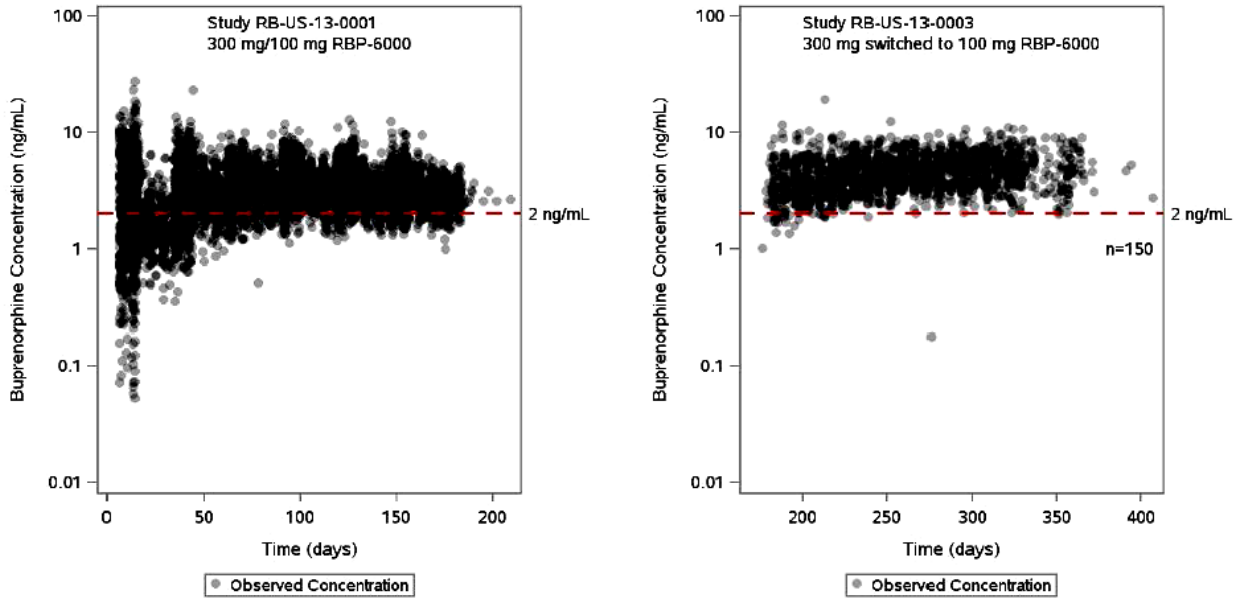
Parameter	Description	Studies RB-US-12-0005 and RB-US-13-0001			Studies RB-US-12-0005, RB-US-13-0001 and RB-US-13-0003		
		Population Value (θ)	Inter-Individual Variability (ω^2)		Population Value (θ)	Inter-Individual Variability (ω^2)	
		Estimate (%RSE)	Estimate (%RSE)	%CV	Estimate (%RSE)	Estimate (%RSE)	%CV
FRK14	Relative change of K14 of SUBUXONE to SUBUTEX	0.898 (28.4)	NA	NA	0.650 (11.2)	NA	NA
FRF1	Relative change of F1 of SUBUXONE to SUBUTEX	1.37 (9.12)	NA	NA	1.47 (3.52)	NA	NA
F1DOSE	Relative change of F1 for dose ≥16mg compared to dose <16mg	0.765 (35.6)	NA	NA	0.765 (FIXED)	NA	NA
BMI on CL	BMI effect on Clearance (power model)	-0.408 (20.8)	NA	NA	-0.364 (20.9)	NA	NA
BMI on K24	BMI effect on fast absorption rate constant from SC depot (power model)	-1.29 (15.0)	NA	NA	-1.32 (13.9)	NA	NA
Sex on K36	Sex effect on slow absorption rate constant from SC depot	0.0759 (139.7)	NA	NA	0.0313 (281.5)	NA	NA
		Residual Variability Estimate (%RSE)			Residual Variability Estimate (%RSE)		
PROP	Proportional residual error	0.190 (0.974)			0.190 (0.658)		
ADD	Additive residual error	0.0378 (13.5)			0.0373 (13.6)		

Source: indv-6000-m05.pdf (sequence 0001), page 36 of 801

[*Reviewer comment: The addition of PK data from study 13-0003 produces comparable PK parameters. Inclusion of PK data from Study 13-0003 improved precision for most parameters which is expected due to the greater pool of data.* ***Overall, the Applicant's population PK analyses reported in report m05 [new parameter estimates model run036_combined (m05) with 13-0003 PK data, VPC for 13-0003 13-0003 PK data using model run036 (from report m04), and diagnostic plots for 13-0003 PK data acquired using final estimates from run036 (from report m04)] further support the acceptability of the final mode from report m04, run036***.]

Applicant provided results of a graphical analysis to compare the PK for the same regimen administered in the two studies (13-0001 versus 13-0003). Applicant concludes that exposures were comparable for patients who received 300 mg / 100 mg regimen in Trial 13-0001 and patients who received the 300 mg / 100 mg regimen in Study 13-0003 (see figure below).

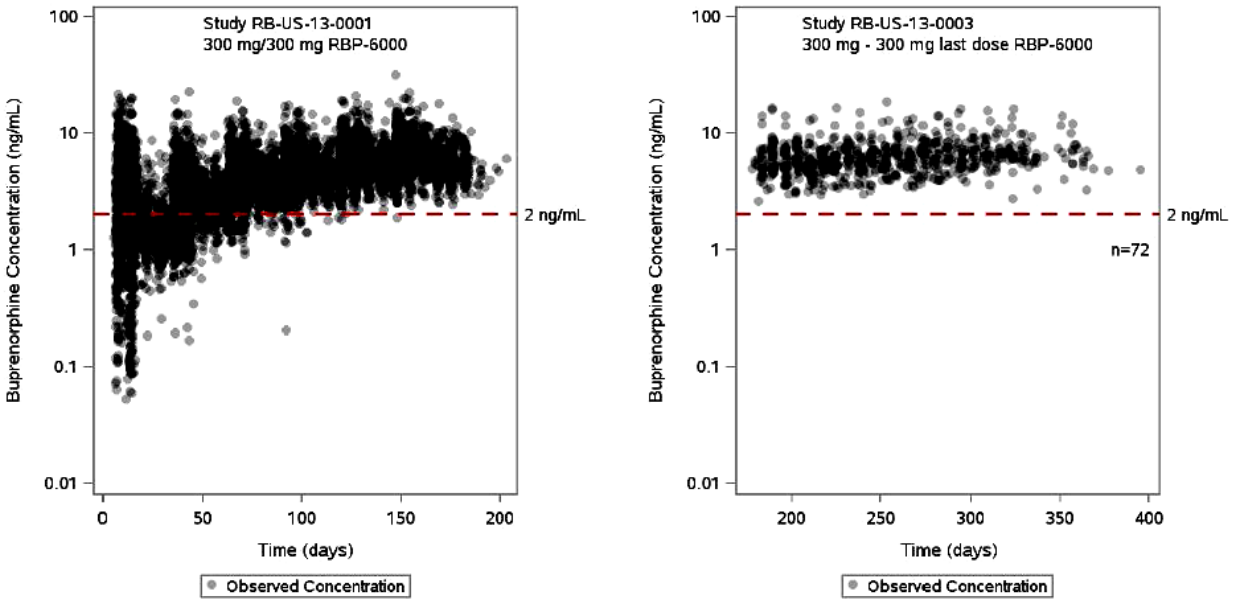
Figure 46: Observed Plasma Concentration Level of Patients who received <u>300 mg / 100 mg</u> dose in Trial 13-0001 (Left Panel) and Patients who Received <u>300 mg / 100 mg</u> in Study 13-0003 (Right Panel).



Source: indv-6000-m05.pdf (sequence 0001), page 27 of 801

Applicant concludes that exposures were comparable for patients who received the 300 mg / 300 mg regimen in Trial 13-0001 and patients who received the 300 mg / 300 mg regimen in Study 13-0003 (see figure below).

Figure 47: Observed Plasma Concentration Level of Patients who received 300 mg / 300 mg dose in Trial 13-0001 (Left Panel) and Patients who Received 300 mg / 300 mg in Study 13-0003 (Right Panel).



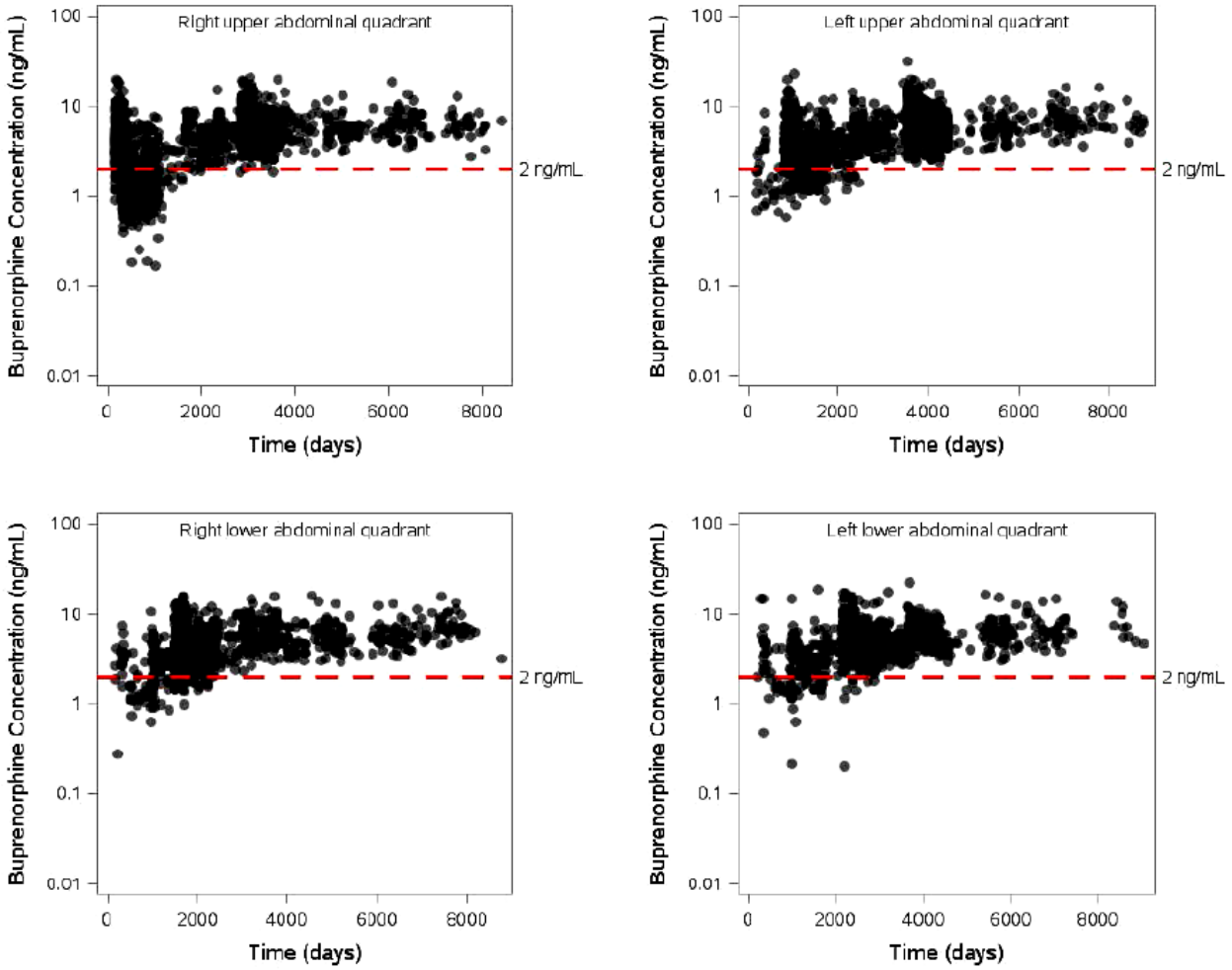
Source: indv-6000-m05.pdf (sequence 0001), page 27 of 801

[*Reviewer comment: The plots in the previous two figures compare PK in Trial 13-0001 versus PK for the same regimen administered the follow-up study 13-0003. The PK profiles in the right panels of the previous two figures (representing study 13-0003) appear to have fewer data points and less dispersion of concentration values. However, study 13-0003 provides one sample every other week. Trial 13-0001 provides rich PK samples which include samples near T_{max} (please refer the review of study M04 in 4.2.1 for details on PK sampling in Trial 13-0001).*

Overall, the plots in the previous two figures indicate that for both regimens administered in Trial 13-0001, consistent PK profile is generated for the same regimen administered in study 13-0003.]

The effect of injection site (right upper abdominal quadrant, left upper abdominal quadrant, right lower abdominal quadrant, left lower abdominal quadrant) on buprenorphine PK was assessed graphically. The Applicant stratified the PK data by injection site and generated a PK plot (see figure below).

Figure 48: Comparison of Plasma Concentration by Injection Site.



Time represents the time after the first RPB-6000 SC injection for each subject.
Source: indv-6000-m05.pdf (sequence 0001), page 29 of 801

The applicant concludes that reinjection into the same abdominal quadrant had no impact on buprenorphine plasma concentration levels.

[*Reviewer comment: Based on the Applicant's analyses, re-injection into the same injection site does not appear to influence systemic buprenorphine exposure.*]

4.2.3 M06 – Ketoconazole effect on PK:

Report M06 is titled "RBP-6000 Project Drug-Drug Interaction Modeling & Simulation for SUBUTEX and RBP-6000 with Ketoconazole". Applicant modelled PK following SL Subutex administration and SC injection of RBP-6000 to estimate SL and SC bioavailability parameters, modelled the effect of ketoconazole with separation of first-pass and systemic clearance, and estimated the effect of ketoconazole on PK following RBP-6000 administration.

Data from the following clinical studies were included in these analyses:

- **RB-US-12-0005 (Phase 2a)**: Study 12-0005 enrolled n=89 subjects into 6 cohorts (14-15 subjects per cohort). One cohort (Cohort 6) received repeat injections of 300 mg SC RBP-6000 every 28 days. Two cohorts (Cohorts 2 and 4) received repeat injections of 100 mg SC RBP-6000 every 28 days. Additional Information regarding study 12-0005 can be found in the section of this review regarding report M04.
- **P01242**: Effects of Ketoconazole on the Pharmacokinetics of Buprenorphine: a Single Center, Phase 1, Open-Label, Fixed Sequence, Drug Interaction Study of Ketoconazole in n=38 Opiate-Dependent Subjects. Subjects were titrated for 4-6 weeks to one of three daily stable doses of SUBUTEX (8 mg, 12 mg or 16 mg of buprenorphine per day) and remained on the same dose for ≥ 2 weeks before entering PK portion of study. Subjects were to remain on the final titrated Subutex dose from at least Day -14 to Day 7. On Days 1 to 6, 400 mg/day ketoconazole was administered orally after Subutex SL administration.
    - **Rich PK** – SL Buprenorphine: On Day -1 (Subutex but no ketoconazole) and again on Day 6 (Subutex after 6 days ketoconazole) PK samples were collected at 0, 0.5, 0.6, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 post-dose.

AUC_{tau} values were measured under steady-state conditions for Subutex in Study P01242. For study 12-0005, Applicant applied Helmert's method (using pre-dose concentration measurements) for assessing steady-state. Applicant concludes that steady-state is achieved by Day 85 (Injection 4) for RBP-6000 300 mg and 200 mg but not for 100 mg. However, Applicant utilized Day 85 $AUC_{Day2-28}$ values from study 12-0005 for 100, 200 and 300 mg SC RBP-6000 every 28 days to build the model.

[*Reviewer comment: $AUC_{Day2-28}$ is effectively AUC_{tau} as the tau was 28 days in study 12-0005.*]

PK Model (M06)

This model utilized AUC values as the dependent variable rather than concentration values. The PBPK model included terms that were unique to Subutex SL, unique to RBP-6000, and components that were common between the two products. Following Subutex SL administration a fraction $F_{abs,SL}$ is absorbed directly into the plasma and 1- $F_{abs,SL}$ is swallowed. Of the Subutex SL administration that is swallowed, the fraction $F_{abs,PO}$ is absorbed, of which a fraction E_G undergoes first-pass effect in the gut (1-E_G passes intact through gut to the liver), and proportion E_H undergoes first-pass effect in the liver (1-E_H passes intact through liver to plasma). Once in the plasma, a fraction f_{met} is metabolized into norbuprenorphine via 3A4 (and 1-f_{met} is metabolized by other pathways). At each step along the way where 3A4-mediated metabolism

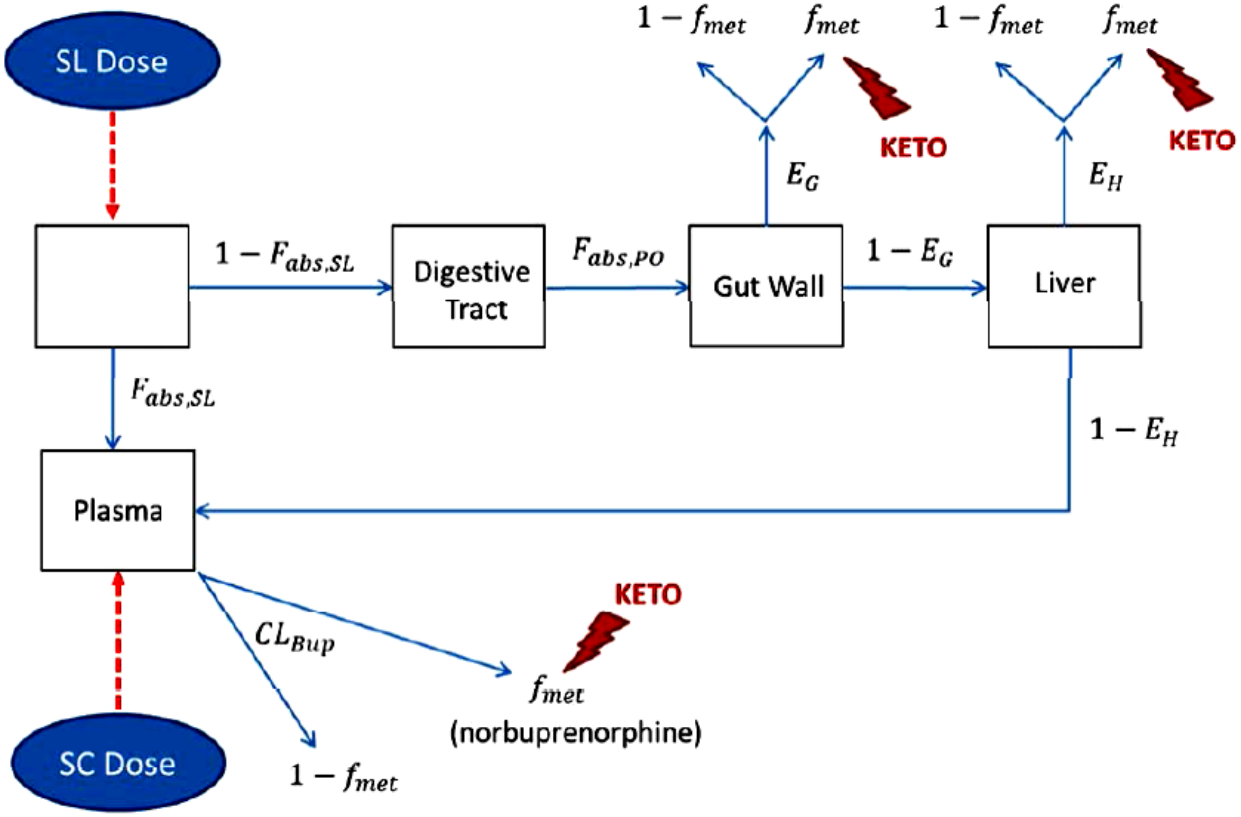
occurs in the gut wall, first-pass in liver, or subsequent passes in the liver, Applicant modeled the effect of ketoconazole on 3A4 mediated metabolism of buprenorphine.

Following RBP-6000 SC injection, the fraction $F_{abs,SC}$ of the injection is absorbed into systemic circulation.

[*Reviewer comment: This model differs from the models in m04 and m05. In this model, both SC and SL absorption are expressed only in terms of extent of absorption (e.g. via bioavailable terms). Models m04 and m05 utilized a first-order absorption model with transit for SL administration and dual first order models with one transit compartment for SC administration. Please refer to discussion at the end of this section for additional information.*]

The structural model is shown in the figure below.

Figure 49: Schematic of PK Model for Disposition of Buprenorphine Following Sublingual and Subcutaneous Administration of SUBUTEX and RBP-6000 Respectively, With and Without Concomitant Administration of Ketoconazole



Source: indv-6000-m06.pdf (sequence 0001), page 11 of 59

The following is a description of the rate constants and overall PK parameters referred to in the figure above:

- KETO: ketoconazole; SC: Subcutaneous; SL: Sublingual.
- $F_{abs,SC}$: Absolute bioavailability of buprenorphine after SC injection
- $F_{abs,SL}$: Fraction of buprenorphine absorbed by SL route after SL administration

- $F_{abs,PO}$: Fraction of buprenorphine absorbed from the digestive tract
- E_G: Gut extraction ratio
- E_H: Hepatic extraction ratio
- CL_{BUP}: Buprenorphine systemic clearance
- f_{met}: Fraction of buprenorphine systemic clearance responsible for the formation of norbuprenorphine.

Inter-Individual Variability: Applicant tested, in a stepwise manner, interindividual variability terms on $F_{abs,SL}$, $F_{abs,SC}$, and CL_{norbup}. Inclusion of an interindividual variability term on $F_{abs,SC}$ provided the greatest decrease in objective function of the 3 terms included in the stepwise assessment. For this reason, the bioavailability following SC administration ($F_{abs,SC}$) was the only term for which interindividual variability was estimated. Applicant

Residual Variability: A proportional error model was used to model residual variability for both buprenorphine and norbuprenorphine.

Parameters Set to Constant Values: E_H and Q_H were fixed based on literature data for hepatic blood flow (Davies and Morris, 1993)3 and hepatic coefficient of extraction for buprenorphine (Kilford et al. 2009)4. The fraction of buprenorphine metabolized (f_{met}) was fixed to 0.63, as estimated from Kilford et al. (2009), so that CL_{Norbup} could be estimated.

Covariates: The only covariate was dose on the $F_{abs,SL}$. .

The applicant conducted the analyses in two steps:
- Step 1: Analysis of control data without ketoconazole
- Step 2: Analysis of all data with and without ketoconazole.

Step 1: Individual AUCs of buprenorphine and norbuprenorphine from Study RB-US-12-0005 following repeated SC injections of RBP-6000 and administrations of SUBUTEX SL tablets were fitted together with individual AUCs of buprenorphine and norbuprenorphine from Study P01242 in the absence of ketoconazole (control data).

The parameter estimates for the final model in Step 1 are shown in the table below.

[3] Davies B, Morris T. Physiological parameters in laboratory animals and humans. Pharm Res. 1993 Jul;10(7):1093-5.

[4] Kilford PJ, Stringer R, Sohal B, Houston JB, Galetin A. Prediction of drug clearance by glucuronidation from in vitro data: use of combined cytochrome P450 and UDP-glucuronosyltransferase cofactors in alamethicin-activated human liver microsomes. Drug Metab Dispos. 2009 Jan;37(1):82-9.

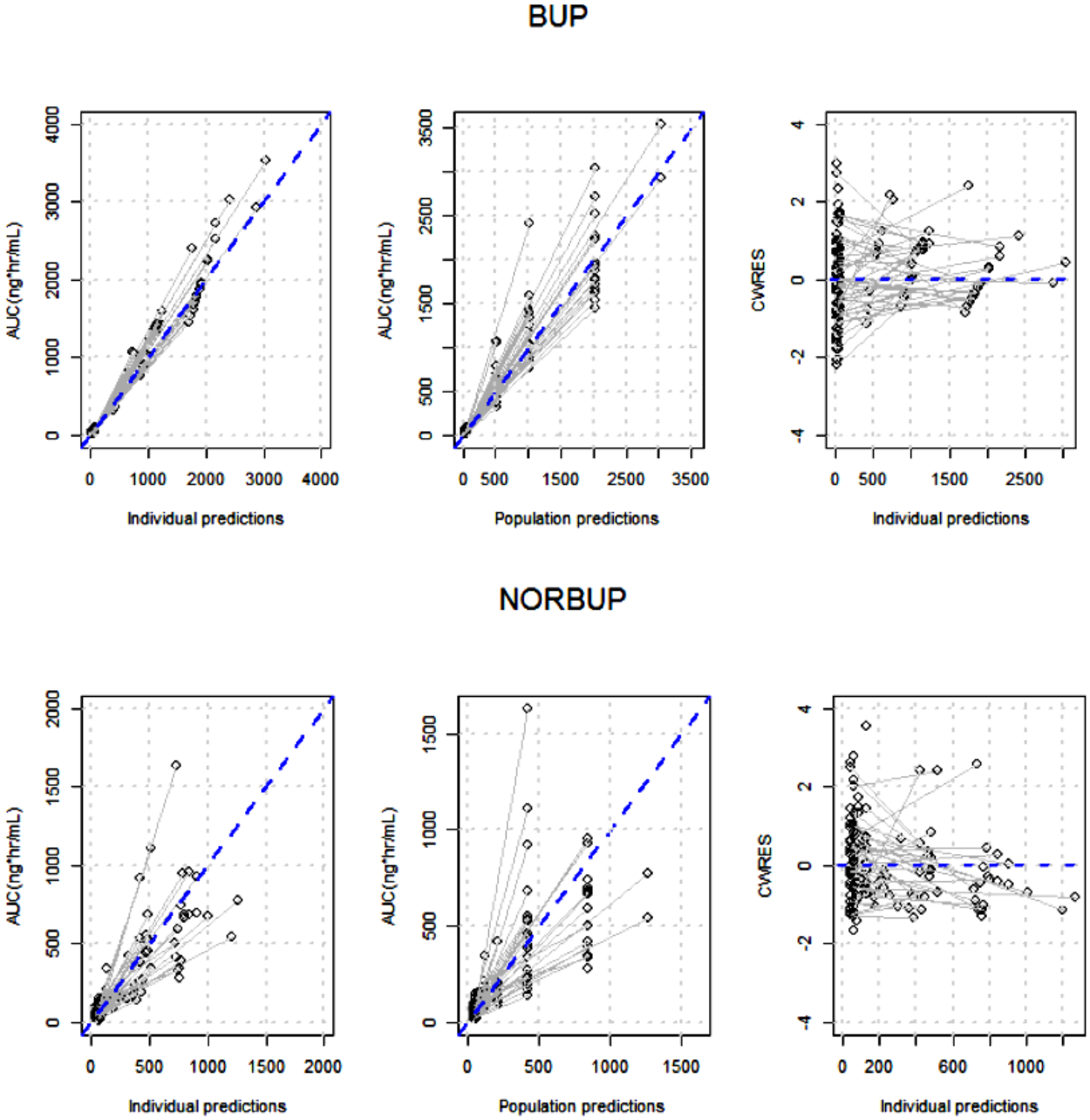
Table 44: Population Pharmacokinetic Parameter Estimates for Analysis Step 1 (Control Data Without Ketoconazole) (Run 03)

	Parameter	Estimate	SE	RSE	
Fixed	fabs_SC	0.7940	0.0010	0.10%	
effect	fabs_PO	1.0000	0.0000	0%	*
	CLnorbup	105.0000	0.8350	0.80%	
	fabs_SL	0.3430	0.0306	8.90%	
	prop err bup	0.2850	0.0023	0.80%	
	prop err norbup	0.4820	0.0039	0.80%	
	Dose eff on FabsSL	0.0226	0.0055	24.30%	
Random	fabs_SC	0.0650	0.0220	33.80%	
*fixed					

Source: indv-6000-m06.pdf (sequence 0001), page 25 of 59

The Applicant performed visual predictive checks using the model and data involved in Step 1.

Figure 50: VPC for Analysis Step 1 (Control Data Without Ketoconazole)(Run 03)



Dashed blue line: identity line or horizontal line for y=0; dots: observed data; grey line: links individual data.
Source: indv-6000-m06.pdf (sequence 0001), page 26 of 59

[*Reviewer comment: Predicted buprenorphine AUC values do not demonstrate any apparent systemic bias with respect to AUC magnitude. However, the predicted norbuprenorphine AUC values appear to be underpredicted by the model in the range of 200 to 1500 ng*hr/ml.*]

Step 2: Individual AUCs of buprenorphine and norbuprenorphine from Study P01242 in the presence of ketoconazole were added to the dataset to estimate the effect of ketoconazole on the

hepatic clearance component responsible for the conversion of buprenorphine to norbuprenorphine. Norbuprenorphine data under ketoconazole were not included in the final analysis as Applicant determined that these data showed an unexpectedly high variability.
In Step 2, initially Applicant utilized the final model in Step 1. Applicant performed another assessment of interindividual variability terms on parameters in a stepwise fashion. The result was that $F_{abs,SC}$ remained as the only term for which interindividual variability was estimated. The parameter estimates for the final model in Step 2 are shown in the table below.

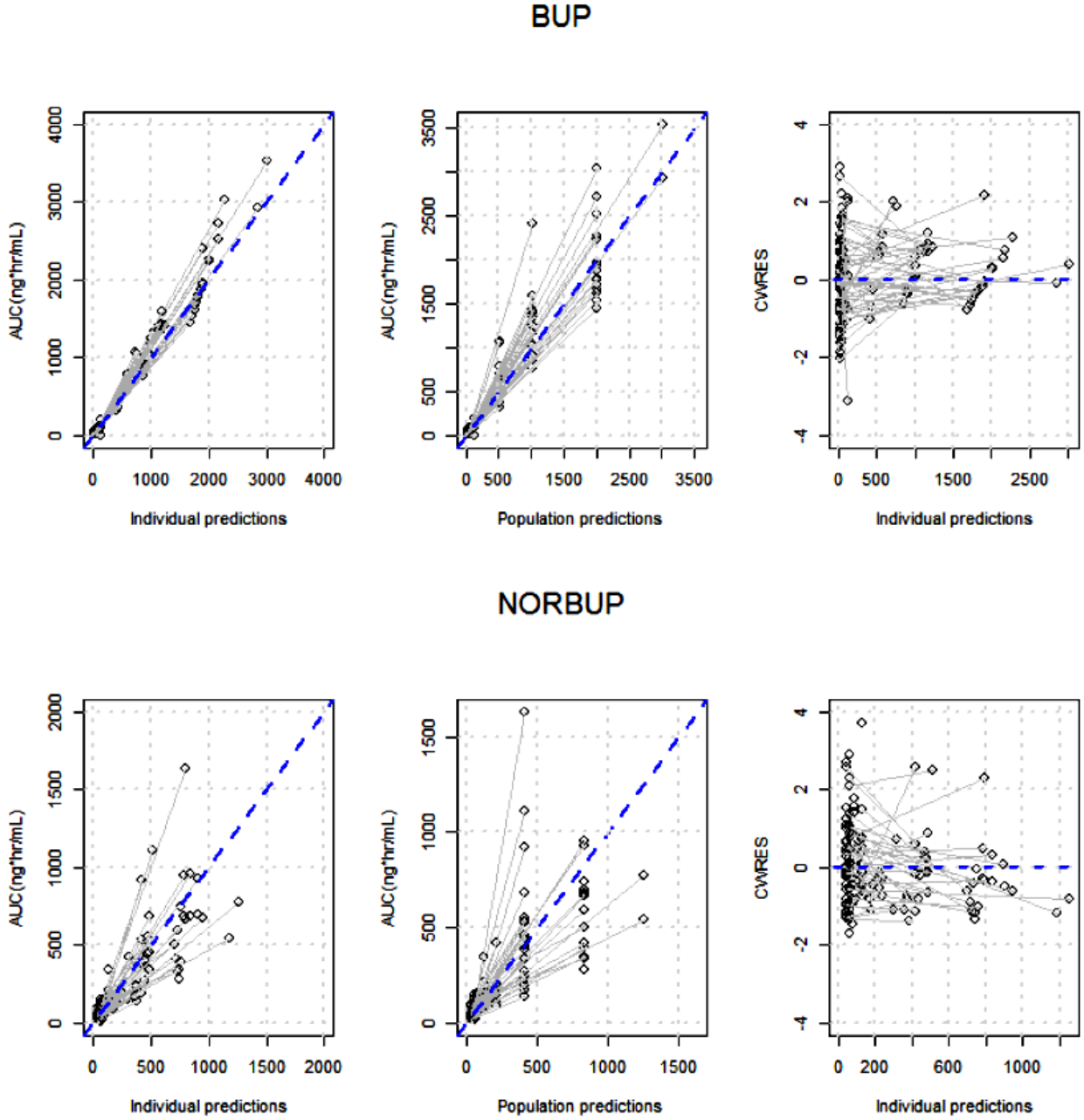
Table 45: Population Pharmacokinetic Parameter Estimates for Analysis Step 2 (Control Data Without Ketoconazole) (Run 06)

	Parameter	Estimate	SE	RSE	
Fixed	fabs_SC	0.7880	0.0280	3.60%	
effect	fabs_PO	1.0000	0.0000	0.00%	*
	CLnorbup	105.0000	4.5800	4.40%	
	fabs_SL	0.3340	0.0294	8.80%	
	prop err bup	0.3070	0.0177	5.80%	
	prop err norbup	0.4650	0.0281	6.00%	
	Dose eff on FabsSL	0.0216	0.0055	25.30%	
	KET	0.5850	0.0591	10.10%	
Random	fabs_SC	0.0797	0.0234	29.40%	
*fixed					

Source: indv-6000-m06.pdf (sequence 0001), page 29 of 59

The Applicant performed visual predictive checks using the model and data involved in Step 2.

Figure 51: VPC for Analysis Step 2 (Control Data Without Ketoconazole)(Run 06)



Dashed blue line: identity line or horizontal line for y=0; dots: observed data; grey line: links individual data.
Source: indv-6000-m06.pdf (sequence 0001), page 26 of 59

[*Reviewer comment: The predicted buprenorphine AUC values do not demonstrate any apparent systemic bias with respect to AUC magnitude. However, similar to the model generated for Step 1, the predicted norbuprenorphine AUC values appear to be underpredicted by the model in the same range of AUC values; 200 to 1500 ng*hr/ml.*]

Simulations to Predict Ketoconazole Effect on SC Administration: Applicant conducted PK simulations to predict the effect of 400 mg ketoconazole per day on buprenorphine exposure following the 4th injection of RBP-6000 100 mg once daily and 300 mg once daily. Four thousand individual AUC values were simulated using the final population parameter values estimated in Step 2. The results of the PK simulations are shown in the table below.

Table 46: Simulated AUC Values for RBP-6000 (100 mg and 300 mg) following 4 SC injections separated by 28 days, With and Without Ketoconazole, for Buprenorphine (BUP) and Norbuprenorphine (NORBUP)

Dose	Analyte	Ketoconazole	Mean AUC (ng*hr/mL)	Std Dev	Median	Minimum	Maximum
100 mg	BUP	Without	930.97	349.73	914.15	111.57	2267.30
		With	1471.63	583.33	1399.90	83.33	3384.10
	NORBUP	Without	394.16	192.91	369.33	2.84	1114.30
		With	162.28	77.51	157.23	0.91	539.81
300 mg	BUP	Without	2824.51	1055.66	2746.65	73.01	6298.70
		With	4507.17	1682.55	4381.00	36.51	10741.00
	NORBUP	Without	1228.56	585.07	1177.50	22.07	3699.00
		With	493.42	254.88	474.71	4.22	1341.70

Source: indv-6000-m06.pdf (sequence 0001), page 33 of 59

The following tables shows the ratio of AUC for RBP-6000 and SL Subutex with and without ketoconazole.

Table 47: Ratio of the Mean Simulated AUC values for RBP-6000 With and Without Ketoconazole, for Buprenorphine (BUP) and Norbuprenorphine (NORBUP)

Dose	Analyte	AUC ratio (with keto/without keto)
100 mg	BUP	1.58
	NORBUP	0.41
300 mg	BUP	1.60
	NORBUP	0.40

Source: indv-6000-m06.pdf (sequence 0001), page 34 of 59

Table 48: Ratio of the Mean Simulated AUC values for SL Subutex With and Without Ketoconazole, for Buprenorphine (BUP) and Norbuprenorphine (NORBUP)

Dose	Analyte	AUC ratio (with keto/without keto)
8 mg	BUP	2.32
	NORBUP	0.54
12 mg	BUP	2.39
	NORBUP	0.55
16 mg	BUP	2.54
	NORBUP	0.56

Source: indv-6000-m06.pdf (sequence 0001), page 34 of 59

Applicant concluded that ketoconazole produces about half the increase in buprenorphine exposure following RBP-6000 administration compared to SL Subutex (e.g. AUC ratio is 2.32 to 2.54 for SL Subutex versus 1.58 to 1.60 for RBP-6000 according to tables above).

[*Reviewer comment: Buprenorphine AUC predictions do not present any apparent bias across the range of AUC values. The visual predictive checks demonstrate that the model under-predicts the norbuprenorphine AUC at values > ~200 ng*hr/mL. The poor performance predicting norbuprenorphine AUC may be due to the Applicant not including norbuprenorphine data under ketoconazole in the final analysis for Step 2 due to an unexpectedly high variability. Overall, the model may not be more adequate for predicting norbuprenorphine AUC.*

This model for report M06 uses a different approach than the population PK models presented in m04 and m05. The population PK models presented in m04 and m05 utilize transit compartments for SL and SC model also includes dual absorption processes. Due to the complex absorption processes for both SL and SC products, directly predicting drug interaction effects on AUC may reduce prediction accuracy. In addition, it is unclear how much the cross-study comparison of Study 12-0005 with Study P01242 may affect the results of these analyses. Furthermore, it is unclear how sensitive the predicted AUC increase due to ketoconazole is to the fixing of certain parameter values.

The model-building process appears reasonable and in general we agree that the effect of ketoconazole on buprenorphine will be less for RBP-6000 compared to SL Subutex. However, due to the aforementioned data limitations, the confidence of the exact drug effect estimate is low. Overall, the certainty in the 58%-60% buprenorphine AUC increase due to ketoconazole is not clear. Even though we may not have confidence in the precision of the AUC increase due to ketoconazole, labeling decisions regarding dose adjustment are adequate to address an AUC increase comparable to the magnitude predicted by the Applicant.]

4.2.4 Reviewer's PK Analyses – Determining PK Profile After Last Injection At Steady-State:

OCP investigated the PK profile after the last injection of RBP-6000 at steady-state. This information was sought to inform a label statement in section 2.4 regarding discontinuation and the duration for which subjects have detectable buprenorphine exposure after discontinuation.

The reviewer conducted PK simulations to determine the concentration profile after the last RBP-6000 injection. The Applicant's population PK model was used to conduct the PK simulations (please refer to section 4.2.1 and 4.2.2 for details). A virtual patient was created to represent the central tendency of the population PK profile. The virtual patient had the median BMI and median weight of the population PK dataset (24.8 kg/m^2 and 75 kg, respectively). As sex is also a covariate, the PK profile of both sexes was simulated.

Following the dosing method utilized in the clinical trials and dosing method proposed for the label, the virtual patient was treated with 2 weeks of SL buprenorphine followed by 2 SC injections of RBP-6000 300 mg separated by a month, then either 100 mg once monthly or 300 mg once monthly. The mean simulated PK profiles for 24 injections (2 years) of 100 mg and 300 mg once monthly maintenance dose regimens are shown in the figures below. As the PK profile is nearly identical between the sexes, only the female PK was plotted in all the reviewer's simulations.

Figure 52: Simulated PK Profile for Initiation with SL Buprenorphine, 2 Injections of 300 mg RBP-6000, and 24 Injections of 300 mg RBP-6000 Once Monthly Maintenance Dosing

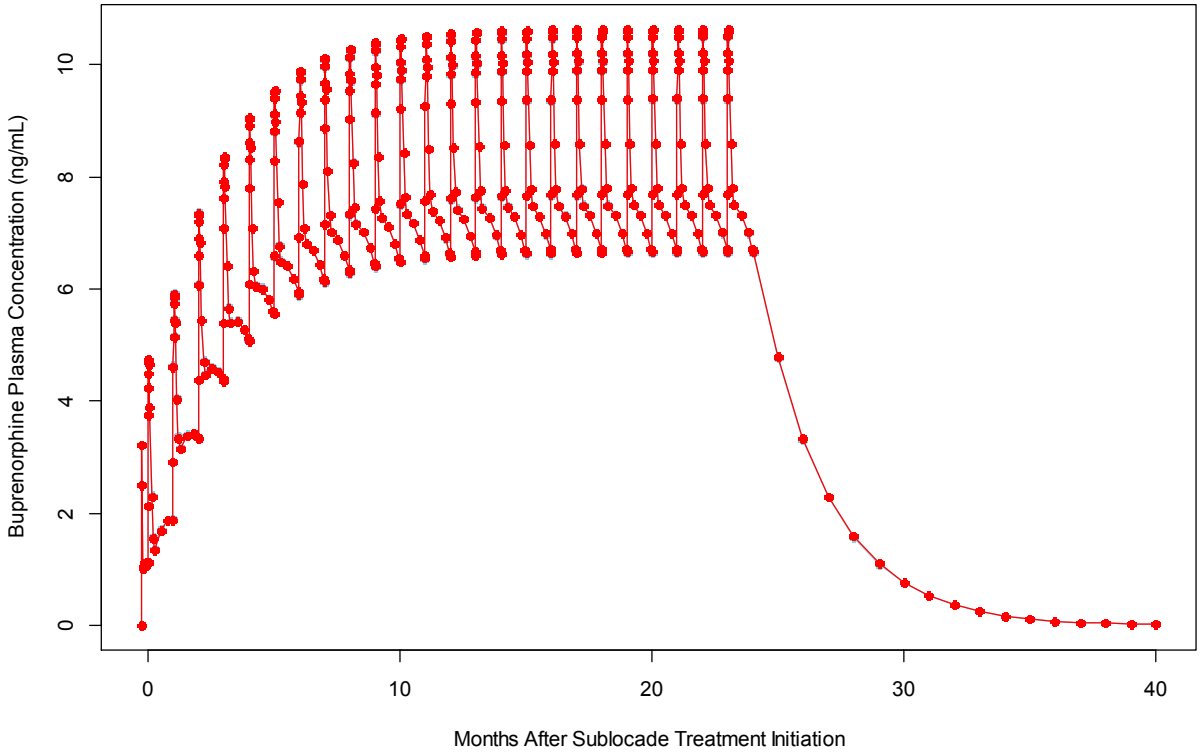
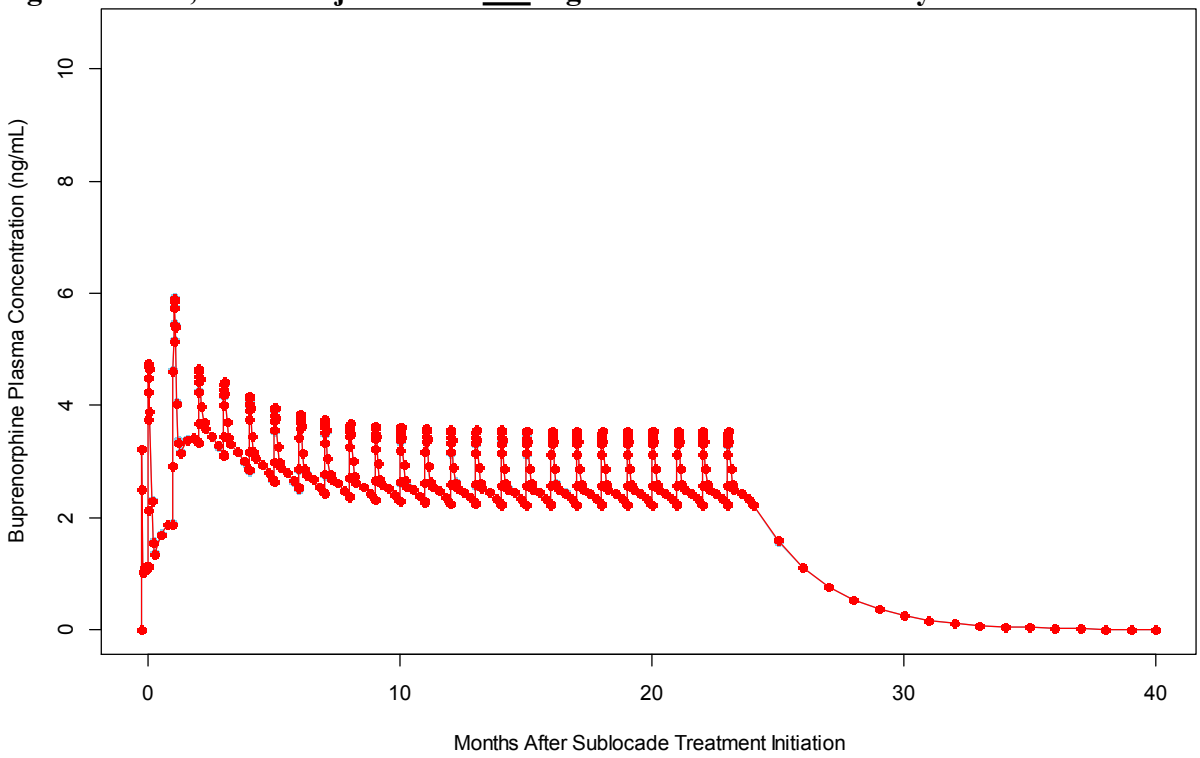
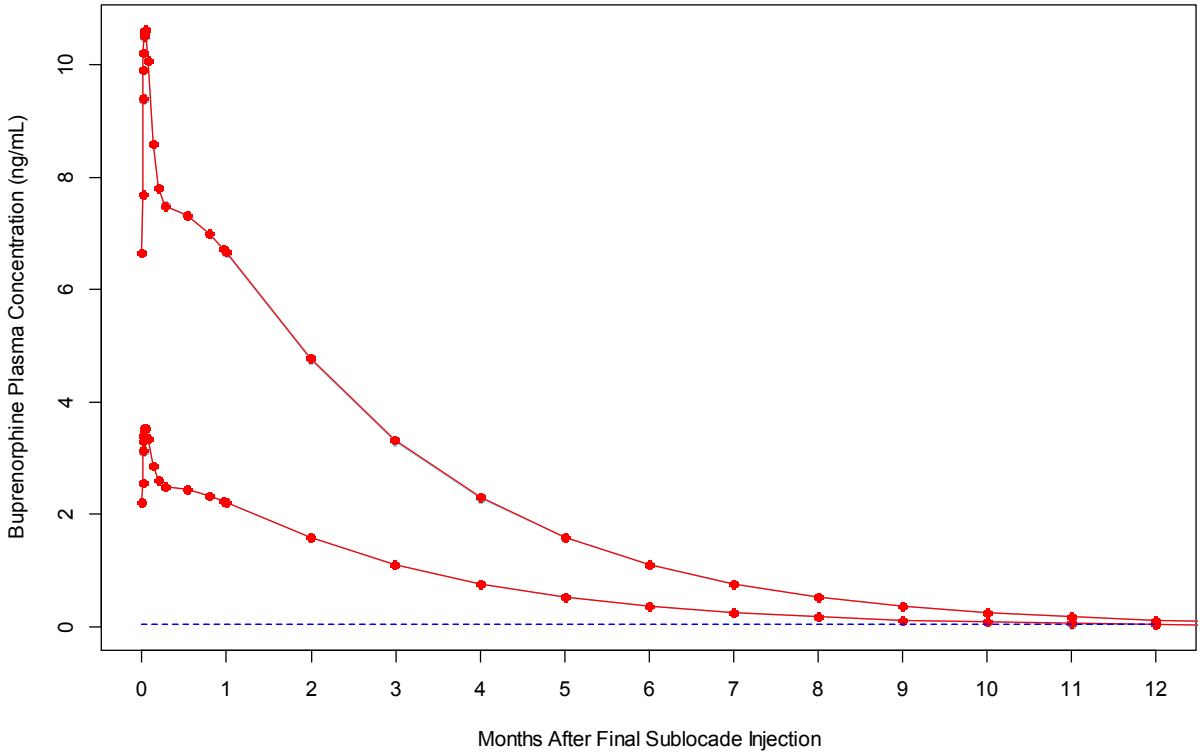


Figure 53: Simulated PK Profile for Initiation with SL Buprenorphine, 2 Injections of 300 mg RBP-6000, and 24 Injections of 100 mg RBP-6000 Once Monthly Maintenance Dosing



In order to better visualize the PK profile after the final injection, the two maintenance dose levels were included on a single plot where time zero is when the final injection occurs (see the figure below).

Figure 54: Simulated PK Profile Following a Final Injection at Steady-State from a 300 mg once monthly Regimen and a 100 mg once monthly RBP-6000 Regimen



Time zero represents the final SC injection of RBP-6000 at steady-state from a 300 mg once monthly regimen (upper red series) and a 100 mg once monthly regimen (lower red series). The blue dashed line represents the analytical assay LLOQ of 0.05 ng/mL.

Overall, for both maintenance dose levels of 100 and 300 mg once monthly, buprenorphine plasma concentration remains above the LLOQ of 0.05 ng/mL for the Applicant's assay for up to 12 months (11 months after discontinuing 100 mg once monthly and 12 months after discontinuing 300 mg once monthly). In section 2.4 of the label a statement was inserted to indicate that the subjects discontinuing RBP-6000 may have detectable plasma levels of buprenorphine for up to 12 months.

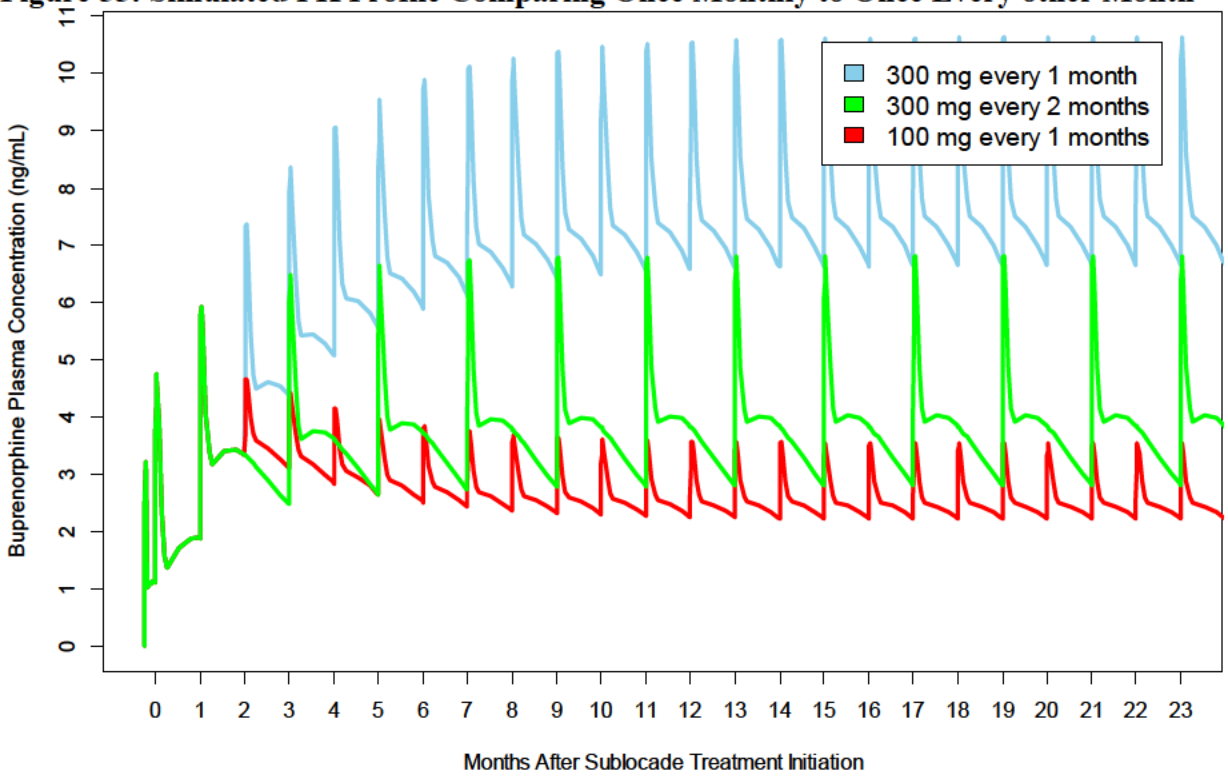
4.2.5 Reviewer's PK Analyses – Assessing Effect of Longer Dose Interval on PK Profile:

Based on the relatively flat PK profile observed after administration of RBP-6000 and due to concerns about safety at the 300 mg maintenance dose, OCP assessed the possibility of a longer dosing interval on RBP-6000 exposure. The reviewer used PK simulations to facilitate this assessment.

The same methodology was used as was described in section 4.3.4 except an additional simulation was assessed for 300 mg once every other month (a regimen that was not studied in the clinical program). Additional dosing intervals were not explored for 100 mg as it would likely result in exposures that are lower than the lowest efficacious dose of 100 mg once monthly.

The following plot shows the comparison of the simulated PK profile for 300 mg once monthly, 300 mg once every other month, and 100 mg once monthly (following 2 weeks SL Subutex induction 10 mg once daily, then 2 initial doses of SC RBP-6000 300 mg spaced 30 days apart).

Figure 55: Simulated PK Profile Comparing Once Monthly to Once Every other Month



The blue, green, and red series represent maintenance doses of 300 mg mg every month, 300 mg every other month, and 100 mg every month. From -0.5 months until 2 months, all 3 series receive the same regimen: 2 weeks of SL Subutex 10 mg, 300 mg SC RBP-6000 at Month 0, 300 mg SC RBP-6000 at Month 1 (which is why all series appear green from Month 0 to Month 2).

Overall, the PK simulations suggest that exposures for a maintenance dose of 300 mg once every other month are likely to be within the range of exposures achieved with maintenance doses of 100 mg once monthly and 300 mg once monthly. As both the 100 and 300 mg once

monthly maintenance dose levels demonstrated efficacy in the pivotal trial, this finding suggests that 300 mg once every other month may be an efficacious dose regimen which could reduce the number of injections by 50% (6 instead of 12 injections per year). Based on discussions with Clinical team, these findings suggest that increased dosing intervals should be explored..

4.3 Exposure-Response and PKPD Analyses

4.3.1 M02 –PKPD Analyses of μ-Opioid Receptor Occupancy in the Brain:

Report M02 is titled "*Modeling of the Relationship Between Buprenorphine Plasma Concentrations and μ-Opioid Receptor Occupancy in the Brain.*" Applicant assessed the relationship between buprenorphine plasma concentration and μ-opioid receptor occupancy (μORO) in the brain. The applicant utilized PK and μORO data from two published clinical trials.

- *Greenwald et al. 2003*[5]: n=5 heroin-dependent subjects were included in the trial. Each subject was successively maintained on 32, 16, 2, and 0 mg daily buprenorphine sublingual tablet doses. Four PET scans with [11C]-carfentanil were conducted on each subject at 4h after the last of 12 daily doses of buprenorphine (32mg, 16mg, 2mg, or placebo). On the 9th day of each maintenance period, blood samples were collected for the measurement of buprenorphine and norbuprenorphine plasma concentrations.
- *Greenwald et al., 2007*[6]: n=10 heroin-dependent subjects were included in the trial. They were initially maintained for ≥ 2 weeks on 16 mg/day buprenorphine given as sublingual tablets. Plasma buprenorphine concentrations, opioid withdrawal symptoms and 4 hydromorphone challenges (24 mg) or 4 PET brain scans with [11C]-carfentanil were conducted at 4, 28, 52 and 76 hours after the last daily buprenorphine dose.

The relationship between μORO and buprenorphine plasma concentration was modelled using an E_{max} structural model in a non-linear mixed effects approach.

$$\mu ORO = \frac{E_{max} \cdot Cp}{EC_{50} + Cp} \quad \text{(equation 1)}$$

where E_{max} is the maximal μORO, C_p is buprenorphine plasma concentration, and EC_{50} is the concentration at which half of the maximal effect is achieved. Residual error was modelled with an additive error model. Inter-individual variability was assessed for EC_{50}. Applicant indicates that the data did not permit the estimation of IIV on Emax.

---

[5] Greenwald MK, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta JK. Effects of buprenorphine maintenance dose on μ-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology. 2003;28(11):2000-9

[6] Greenwald MK, Johanson CE, Bueller J, Chang Y, Moody DE, Kilbourn M, Koeppe R, Zubieta JK. Buprenorphine duration of action: μ-opioid receptor availability and pharmacokinetic and behavioral indices. Biol Psychiatry. 2007;61(1):101-10

[*Reviewer comment: Due to the sparse data at the highest occupancies, precision of an IIV term for E_{max} would be poor. The decision to fix E_{max} IIV to zero is acceptable.*]

The final model estimates are presented in the table below.

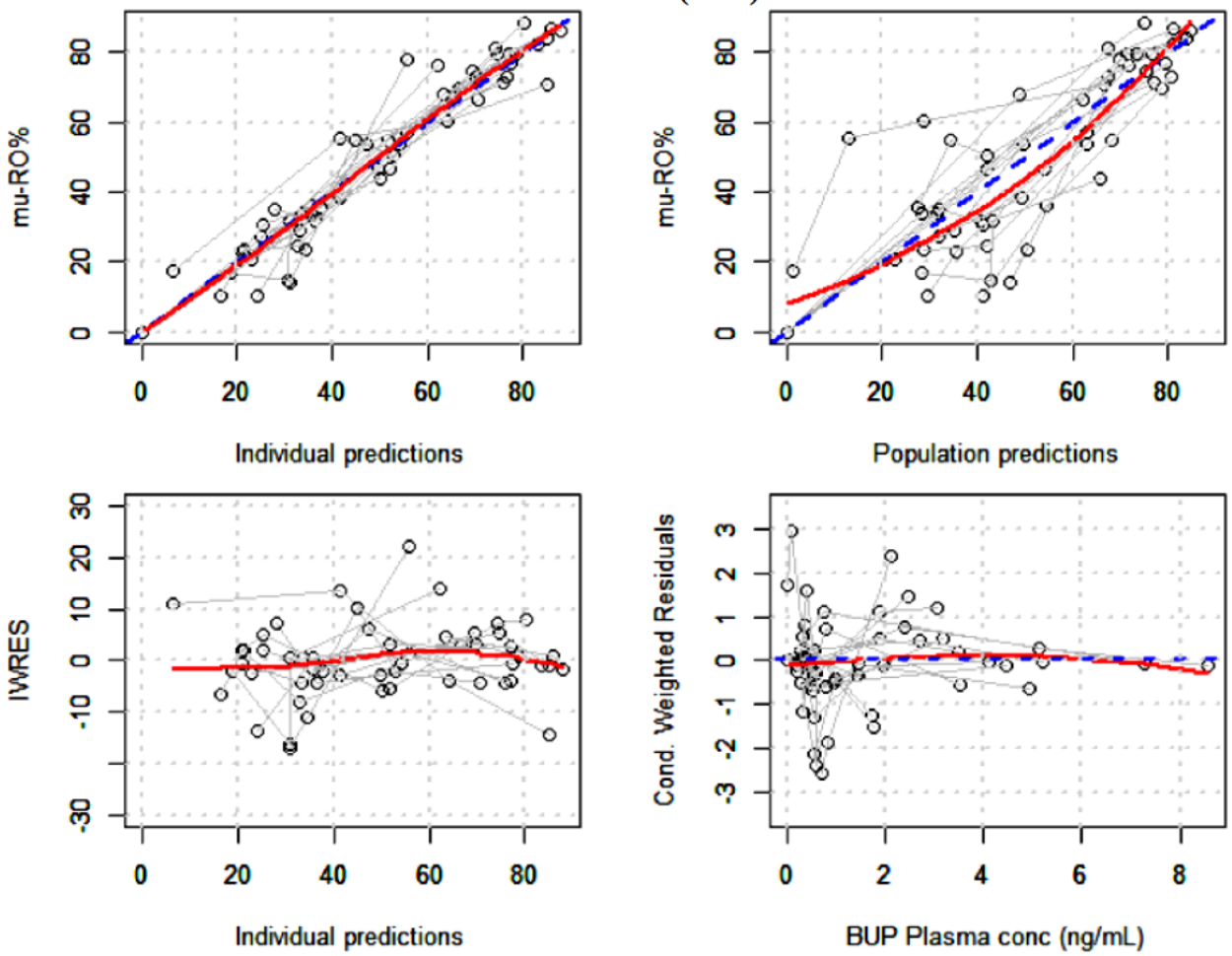
Table 49: Final Population Parameter Estimates for E_{max} Model Relating µORO to Buprenorphine Plasma Concentration (M02)

	Emax	EC50	IIV-EC50	Add Err
Parameter estimates	91.40	0.67	0.47	62.50
Standard errors	3.90	0.19	0.25	22.20
RSE(%)	4.30	28.40	54.30	35.50
95% Conf. Interval	83.76-99.04	0.30-1.04		

source: Indv-6000-m02.pdf (sequence 0001), page 9 of 47

The diagnostic plots are presented below.

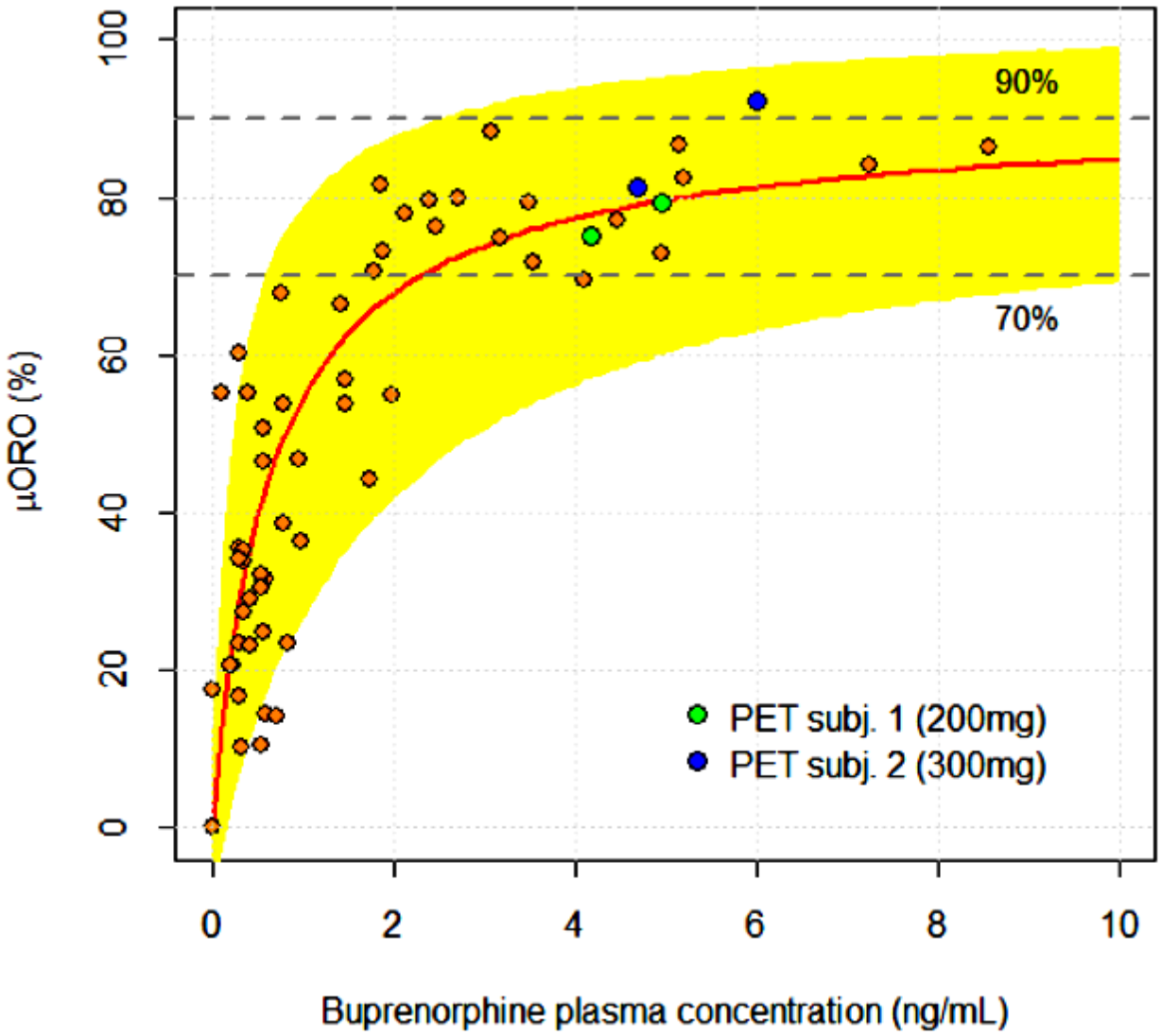
Figure 56: Diagnostic Plots for E_{max} Model Relating μORO to Buprenorphine Plasma Concentration (M02)



source: Indv-6000-m02.pdf (sequence 0001), page 10 of 47

The Applicant conducted a visual predictive check (VPC) as is shown in the figure below. In addition to the data from the literature (red dots), Sponsor superimposed the μORO data and associated buprenorphine concentrations acquired from the n=2 subjects in the PET substudy of study 12-0005 (green and blue dots).

Figure 57: VPC for E_{max} Model Relating μORO to Buprenorphine Plasma Concentration (M02)



source: summary-clin-pharm.pdf (sequence 0001), page 67 of 148

[*Reviewer comment: There is no systematic bias present in the diagnostic plots across the range of observed concentrations. The residuals do not appear to be unbalanced around zero. The visual predictive check plot appears to represent the data well for both the subjects from the literature (red dots) and the n=2 subjects from the PET sub-study in Study 12-0005 (green and blue dots).* ***Overall, the Applicant's model is acceptable.***]

4.3.2 M04 - PKPD Analyses of Illicit Opioid Use, Drug Craving:

Report M04 is titled "*RBP-6000: POPULATION PHARMACOKINETIC/PHARMACODYNAMIC MODELING ANALYSES - Population Pharmacokinetic and Exposure-Response Analyses for Buprenorphine after Repeated Subcutaneous Injections of RBP-6000 in Treatment-Seeking Subjects with Opioid Use Disorder.*" Applicant conducted population pharmacokinetic and exposure-response analyses for buprenorphine following repeat sub-cutaneous injections of RBP-6000 in treatment seeking subjects with opioid use disorder. The purpose of these analyses is to provide evidence-based support for dosing regimens and identify potential dose adjustments for specific patient subpopulations in order to achieve the intended target therapeutic effect.

This section will discuss the population PKPD and exposure-response model. For the population PK analyses provided in M04, please refer to section 4.3 of this review.

Using PK and PD data, applicant developed models to relate buprenorphine exposure to use of illicit opioids and drug craving. Applicant conducted graphical analyses to explore the effect of buprenorphine exposure on withdrawal symptoms.

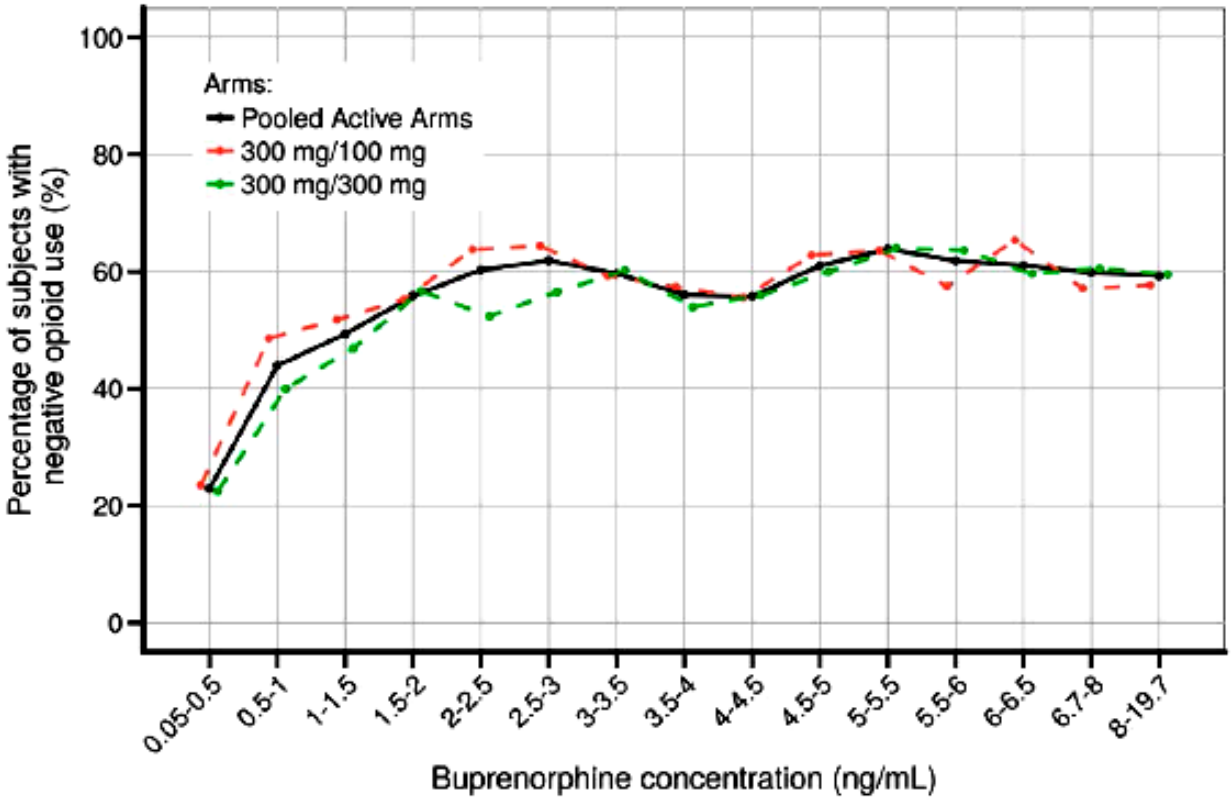
Data from the following clinical trial were included in the analyses:

- **RB-US-13-0001 (Phase 3)**: The schedule for efficacy assessments is summarized below. Please refer to the M04 portion of section 4.3 in this review for additional details on this trial.
    - Urine Drug Screen: Urine drug screens and self-reports were assessed at screening, and then on a weekly basis following each SC injection of RBP-6000 or placebo (Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, 106, 113, 120, 127, 134, 141, 148, 155, 162 and 169), as well as at the safety follow-up visit (Day 197). Urine drug screens were also assessed on the day after each SC injection at 24 hours post-dose (Days 2, 30, 58, 86, 114 and 142).
    - Craving and Withdrawal: Scores for Opioid Craving VAS, COWS and SOWS were measured at the same times as UDS (with the exception of the follow-up visit on Day 197). Opioid craving was additionally measured during the dose adjustment period with SUBOXONE film (Days -8, -4 and/or -1). The COWS and SOWS scores were measured during both induction and dose adjustment with SUBOXONE film (Days -14, -13,-12,-11,-8, -4 and/or -1).
    - Assessments were to be performed prior to each SUBOXONE SL film dosing and at approximately the same time each day (±2 hours) on each planned visit day to the center.

PKPD Model for Illicit Opioid Use (m05)

Use of illicit opioids was modelled as a binary variable (0 is negative or no illicit opioid use; 1 is positive or confirmed illicit opioid use). If both self-reporting and urine drug test are negative than a patient is reported to have a value of zero illicit opioid use. If at least 1 of the two reports are negative (self-report and/or urine drug test) then the patient is reported to be positive for illicit opioid use. The observed data for illicit opioid use versus buprenorphine concentration by arm is presented in the figure below.

Figure 58: Relationship Between the Percentage of Subjects with Negative Opioid Use and Buprenorphine Plasma Concentration (Study RB-US-13-0001)



Solid black curve; percentage of subjects with negative opioid use from the pooled 300 mg/300 mg and 300 mg/100 mg treatment arms. Dashed curves: percentage of subjects with negative opioid use in the 300 mg/300 mg arm (green curve) and 300 mg/100 mg arm (red curve)

Source: indv-6000-m04.pdf (sequence 0001), page 74 of 487

The binary drug use data were analyzed using logistic regression. For observation Y_{ij} in subject i at time t_{ij} ($j=1,\ldots,n_i$), the probability of negative opioid use was represented as:

$$logit\left[P(Y_{ij}=0)\right] = \alpha + fd + \eta_i \quad \text{(equation 2)}$$

$$P(Y_{ij} = 0) = \frac{(exp^{(\alpha + fd + \eta_i)})}{(1 + (exp^{(\alpha + fd + \eta_i)}))})$$ (equation 3)

, where α is the baseline value (intercept) in absence of buprenorphine treatment, f_d is the drug effect , and η_i represents the subject-specific random effect (e.g. between subject variability). An E_{max} model was selected to presents the effect of buprenorphine on probability of negative opioid use (f_d):

$$fd = \frac{E_{max,i} \times C_{p,ij}}{EC_{50,i} + C_{p,ij}}$$ (equation 4)

, where $C_{p,ij}$ is the buprenorphine plasma concentration in subject i at time t_{ij} , $E_{max,i}$ is the maximal drug effect in subject i, and $EC_{50,i}$ is the buprenorphine plasma concentration yielding 50% of the maximal drug effect in subject i.

In the final model, interindividual variability terms were included on α, E_{max}, and EC_{50}. Covariates on α included TC genotype as well as TT genotype (for SNP rs678849 on the delta-opioid rector; OPRD1). Covariates on EC_{50} included users of opioids by injectable route, TC genotype, TT genotype, and race (Black/African American versus non-Black/African American). Covariates on E_{max} include employment status (employed versus non-employed) and race (Black/African American versus non-Black/African American). The parameter estimates for the final model are shown in the table below.

Table 50: Parameters Estimates for the Final PKPD Model (run8.mod) for Illicit Opioid Use in Study RB-US-13-0001.

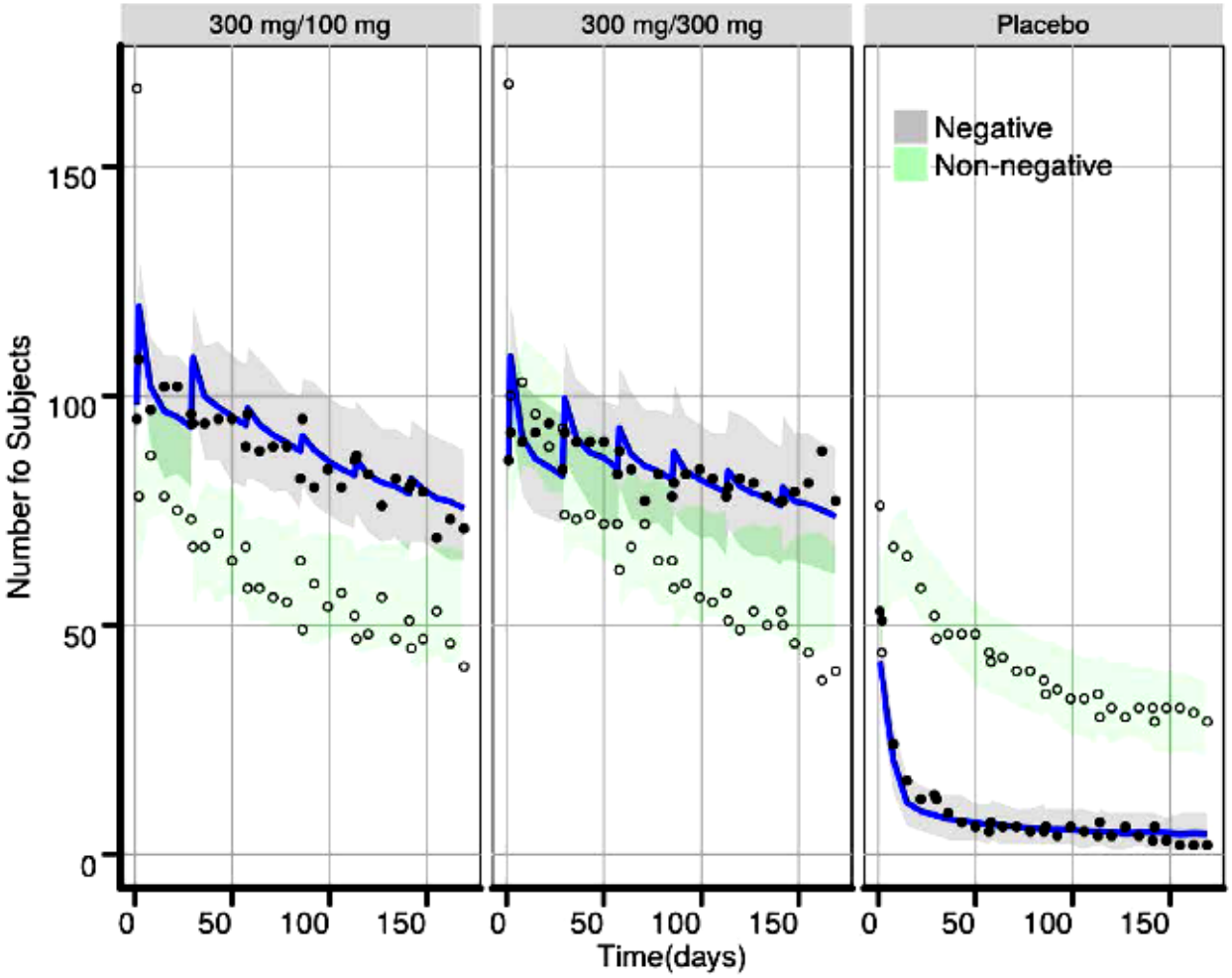
PARAMETERS	DESCRIPTIONS	ESTIMATES (RSE%)	VARIANCE (RSE%)	SD or IIV(%)
θ_α	The baseline logit for Arms 2 and 3)	-3.3 (16)	6.97 (12)	2.64 (SD)
θE_{max}	Maximal drug effect	4.86 (9.7)	0.139 (63)	38.7
θEC_{50}	Concentration yielding half of E_{max}	1.21 (44)	1.19 (0.77)	151.2
θ_{Arm1}	Relative intercept for Arm1 compared to Arms 2 and 3	0.794 (10)		
$\theta_\alpha(OPRD1_2)$	Fractional change in α for TC genotype of OPRD1(rs678849)	0.133 (150)		
$\theta_\alpha(OPRD1_3)$	Fractional change in α for TT genotype of OPRD1(rs678849)	0.309 (92)		
$\theta EC_{50}(INJUSE)$	Fractional increase of EC_{50} for users of opioids by injectable route	2.57 (47)		
$\theta EC_{50}(OPRD1_2)$	Fractional decrease of EC_{50} for TC genotype of OPRD1(rs678849)	-0.713 (19)		
$\theta EC_{50}(OPRD1_3)$	Fractional decrease of EC_{50} for TT genotype of OPRD1(rs678849)	-0.937 (4)		
$\theta EC_{50}(RACE)$	Fractional decrease of EC_{50} for Blacks/African Americans	-0.113 (910)		
$\theta E_{max}(EMPLY)$	Fractional increase of E_{max} for employed vs. unemployed subjects	0.427 (37)		
$\theta E_{max}(RACE)$	Fractional decrease of E_{max} for Blacks/African Americans	-0.311 (31)		

Source: indv-6000-m04.pdf (sequence 0001), page 89 of 487

Applicant indicates that major EC_{50} covariates were use of opioids by injectable route (3.6 times higher EC_{50} for users of injectable route opioids). Subjects with the TC and TT genotype has their EC_{50} reduced by 71% and 94% respectively. Subjects that were employed at baseline showed 43% higher E_{max} and Black/African American subjects showed a 31% lower maximal drug efficacy compared to non-Black/African Americans.

A visual predictive check was performed for the number of subjects with negative opioid use per treatment arm in study 13-0001.

Figure 59: VPC for Number of Subjects with Negative Opioid use Per Treatment Arm in Trial 13-0001.



White circles and black dots: Observed percentages. Blue line: Median model prediction. Shaded gray or green area: 95% confidence interval for model predictions.

Source: indv-6000-m04.pdf (sequence 0001), page 85 of 487

[*Reviewer comment: The VPC indicates that the model represents the data well. The precision is poor for the estimate of TC effect on α, TT effect α, and race on EC_{50} (150%, 92%, and 910%, respectively).* ***Other than these 3 covariates with poor precision, the Applicant's PKPD model for illicit opioid use is acceptable.***

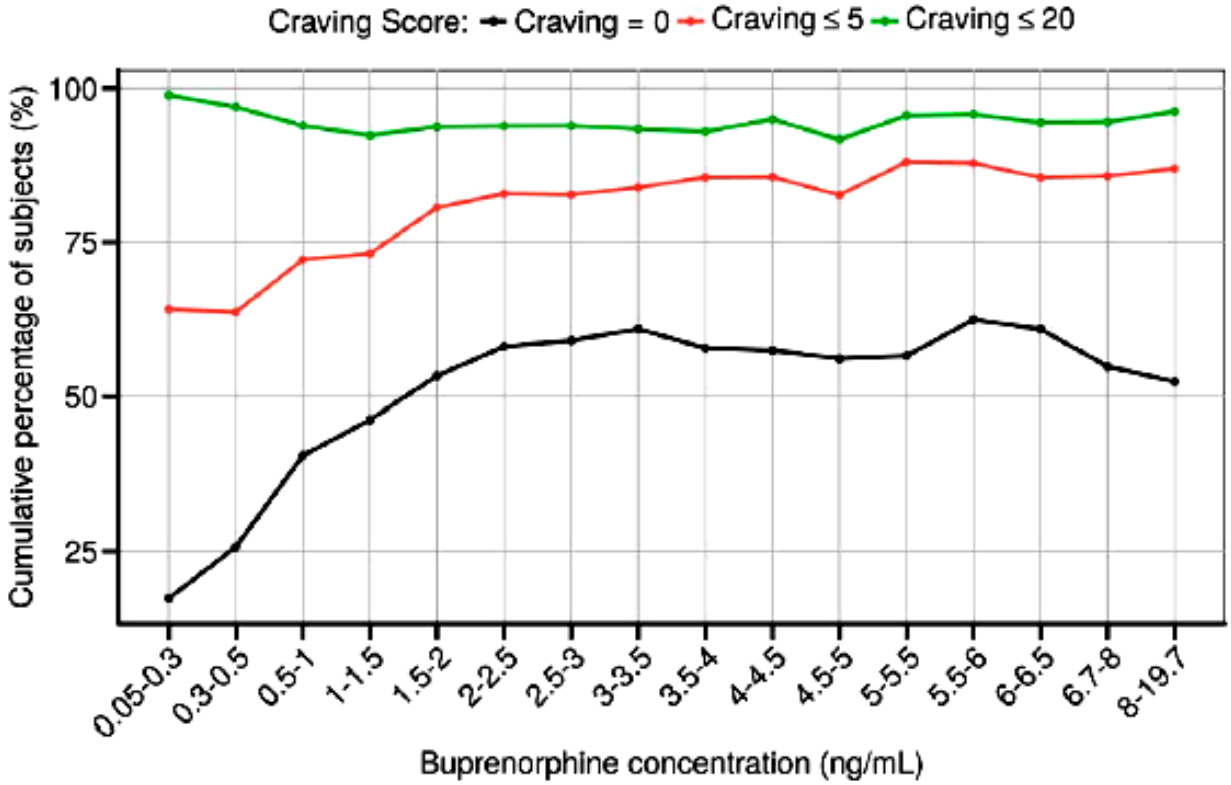
While the effects of other covariates are estimated with greater precision, Applicant has not proposed any dose adjustments based on any covariates in this model. The reviewer agrees no dose adjustments will be necessary based on the covariates in this model as the recommended

dose strategy is to use the low maintenance dose (100 mg once monthly) and proceed to the high maintenance dose (300 mg once monthly) if tolerability permits and if the subject is not achieving sufficient benefit from the lose maintenance dose.]

PKPD Model for Opioid Craving (m05)

Opioid craving was assessed using the visual analog scale (VAS) score (0 mm is neutral craving, 100 mm is maximum craving). Craving was categorized by score (category 1: 0 mm, category 2: 1-5 mm, category 3: 6-20 mm and category 4: >20 mm) for the purpose of PKPD analysis. Applicant selected 20 mm as a threshold for clinical relevance. Selection of other 3 categories was data driven in order to achieve a sufficient proportion of patients in each category. The observed data for drug craving versus buprenorphine concentration by arm is presented in the figure below.

Figure 60: Relationship Between the Percentage of Subjects in Each Category of Opioid Craving VAS Score and Buprenorphine Plasma Concentration (Study RB-US-13-0001)



Curves: percentage of subjects with a craving score of zero (black curve), below 5 (red curve) and below 20 (green curve) form the pooled 300 mg/300 mg and 300 mg/100 mg treatment arms.

Source: indv-6000-m04.pdf (sequence 0001), page 75 of 487

The ordinal data were analyzed using logistic regression. For observation Y_{ij} in subject i at time t_{ij} (j=1,…,n_i), the probability for Y_{ij} to be lower than or equal to category "m" (where category m=1,2 or 3) is expressed as:

$$logit\,[P(Y_{ij} \leq m)] = \alpha_m + fd + \eta_i$$ (equation 5)

, where α_m is the baseline value (intercept) in absence of buprenorphine treatment, f_d is the drug effect, and η_i represents the subject-specific random effect (e.g. between subject variability). An E_{max} model was selected to presents the effect of buprenorphine on probability of negative opioid use (f_d) (same structure as the E_{max} applied in the illicit opioid use PKPD model). As the data are ordinal, alpha values were constrained such that $\alpha_1 < \alpha_2 < \alpha_3$. The probability of observing a score in a given category is expressed as:

$$P(Y_{ij} = 1) = P(Y_{ij} \leq 1)$$ (equation 6)

[*Reviewer comment: As category m=1 is the lowest category, then it is acceptable to set probability that Y_{ij}=1 equal to the probability that $Y_{ij} \leq 1$.*]

$$P(Y_{ij} = 2) = P(Y_{ij} \leq 2) - P(Y_{ij} \leq 1)$$ (equation 7)

$$P(Y_{ij} = 3) = P(Y_{ij} \leq 3) - P(Y_{ij} \leq 2)$$ (equation 8)

$$P(Y_{ij} = 4) = 1 - P(Y_{ij} \leq 3)$$ (equation 9)

In the final model interindividual variability terms were included on α_1, E_{max}, and EC_{50}. A term was included to represent the effect of arm assignment on baseline value for craving (e.g. arm 1, 300/100 arm versus Arms 2 and 3, 300/300 arm and placebo arm, respectively). The only covariate was baseline BMI on E_{max}. The final parameter estimates are shown in the table below.

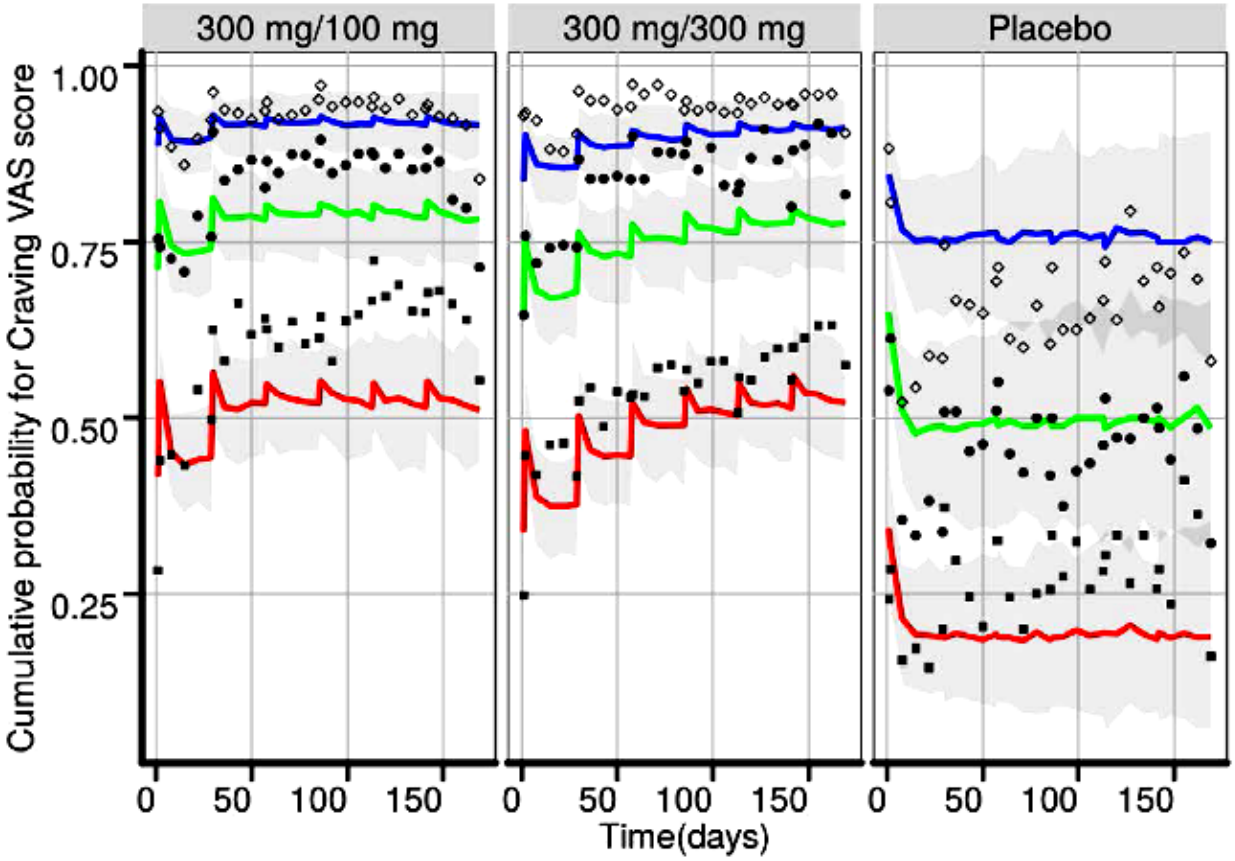
Table 51: Parameters Estimates for the Final PK/PD model (run06.mod) for Opioid Craving in Study RB-US-13-0001

PARAMETERS	DESCRIPTIONS	ESTIMATES (RSE%)	VARIANCE (RSE%)	SD or IIV(%)
α_1	Baseline value (intercept) of the logit for craving=0 (Arms 2-3)	-2.41 (6.8)	4.42 (9.3)	2.1 (SD)
$\alpha_{1,Arm1}$	Baseline value (intercept) of the logit for craving=0 (Arm 1)	-1.87 (11)		
δ_1	Delta between α_2 and α_1	2.28 (1.7)		
δ_2	Delta between α_3 and α_2	1.85 (2.5)		
E_{max}	Maximal drug effect	2.87 (7.2)	0.7 (14)	101
EC_{50}	Concentration yielding half of E_{max}	2.45 (15)	0 (FIXED)	0 (FIXED)
θ_{BMI}	Exponent of the power model relationship between E_{max} and BMI	0.853 (37)		

**The δ terms are included to ensure that α1 < α2 < α3 (e.g. α2 = α1+ δ1, α3 = α2+ δ2; where δ1 and δ2 are both positive)*
Source: indv-6000-m04.pdf (sequence 0001), page 94 of 487

A visual predictive check was performed for the proportion of subjects with zero craving, craving below 5, and craving below 20 per treatment arm in study 13-0001.

Figure 61: VPC for Proportion of Subjects with Zero Craving, Craving Below 5, and Craving Below 20 per Treatment Arm in Study 13-0001



The white squares and black points/squares are observations. Bold curves are median model predictions for craving = zero (red), craving below 5 (green), and craving below 20 (blue). Shaded grey area: 95% confidence intervals for model predictions.

Source: indv-6000-m04.pdf (sequence 0001), page 97 of 487

[*Reviewer comment: The Applicant indicates that the differing baseline terms were the result of differing cumulative probabilities for craving in Arms 1 and 2 despite the first two injections having equal value (300 mg and 300 mg) and comparable exposure. Thus, it is not clear why the baseline risk values were different in arm 1 versus the other arms. While the BMI covariate was statistically significant, BMI only explains 1% of the craving variability. The VPC appears to systematically under-predict the drug-liking score for both RBP-6000 arms for all 3 ranks of drug-craving. For the placebo arm, the model appears to under-predict the zero craving (red series) and over-predict the craving below 20 (blue series). The reason for these under-predictions and over-predictions is not clear.*

The Applicant indicates that the relatively wide 95% CI for placebo (compared to RBP-6000 arms) is due to lower sample size in placebo arm compared to RBP-6000 arms, which is reasonable.

The reviewer agrees with the Applicant that the effect of BMI on drug craving is not clinically relevant and does not need to be considered for dose selection. ***Overall, the Applicant's PKPD model for drug craving does not appear to adequately predict drug craving for subjects treated with RBP-6000 or placebo***.]

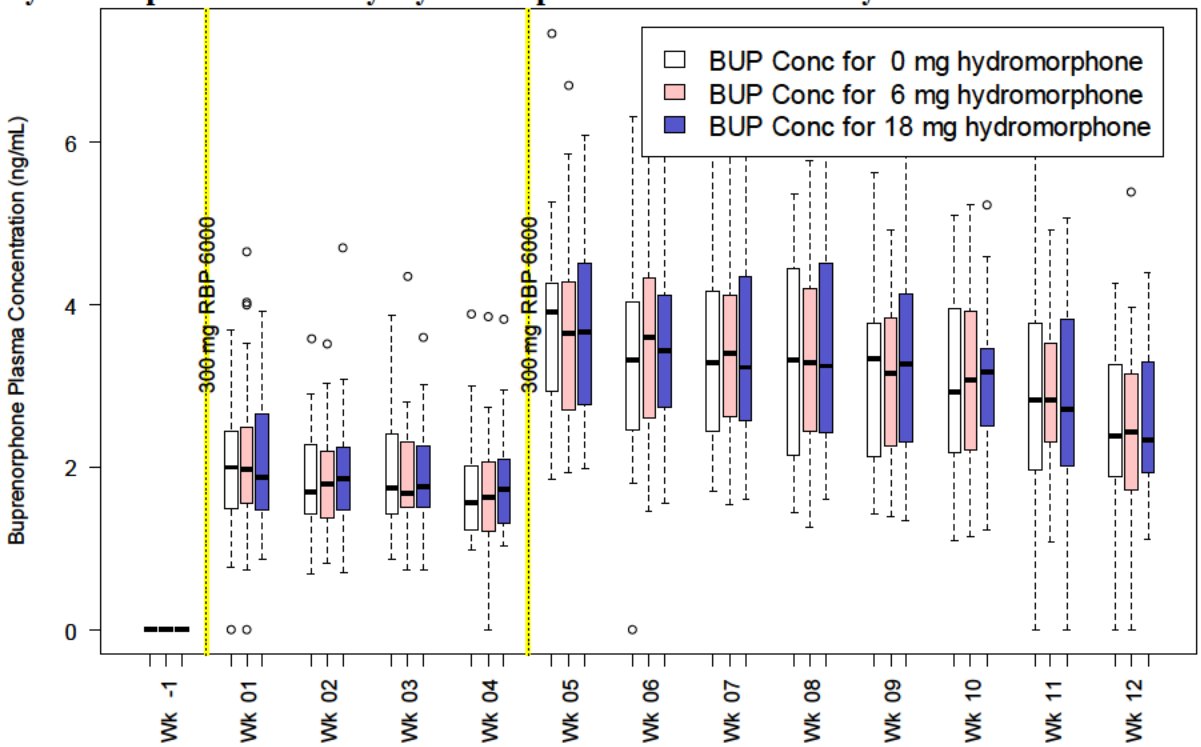
4.3.3 Reviewer's PKPD Analyses of Drug-Liking Data from Blockade Study 13-0002:

The blockade study 13-0002 was a pivotal piece of support for the approval of RBP-6000. The review team expressed concerns regarding the conduct of Study 13-0002 (please refer to the AC presentation by the CSS reviewer and Statistics reviewer for additional information). One relevant concern was that the mean drug-liking score over a 300-minute testing session was used in the statistical analyses. The review team decided that the maximum drug liking score was the more appropriate measure. Analyses were conducted to assess the relationship between the maximum (E_{max}) drug liking score and buprenorphine exposure following RBP-6000 administration. These analyses were performed to provide additional context to the statistical issues during the review of the blockade study.

PK and PD data were available from n=38 subjects in study 13-0002, the blockade study. The blockade study assessed the effect of buprenorphine on the measure of how much a subject "likes" hydromorphone. Each week there was a hydromorphone testing session wherein single dose of hydromorphone (0, 6, or 18 mg) was administered once per day for 3 consecutive days in a blinded randomized manner. The Applicant's analyses subtracted the drug-liking score from "placebo (0 mg hydromorphone)" from the drug-liking score for 6 mg and 18 mg hydromorphone doses administered in each 3-day testing session each week. One hydromorphone session was conducted in the absence of buprenorphine and 12 hydromorphone sessions, once session per week for 12 weeks. RBP-6000 300 mg was administered prior to the Week 1 hydromorphone session and prior to the Week 5 hydromorphone session (2 injections spaced 4 weeks apart). On the weeks of RBP-6000 SC injection, hydromorphone challenges started 4 days after SC injection. Please refer to section 2 of this review for additional information on study 13-0002.

PK data were buprenorphine plasma concentrations measured immediately before the hydromorphone challenge. The figure below shows the distribution of buprenorphine plasma concentrations at each week where SC RBP-6000 300 mg was administered prior to week 1 and prior to week 5.

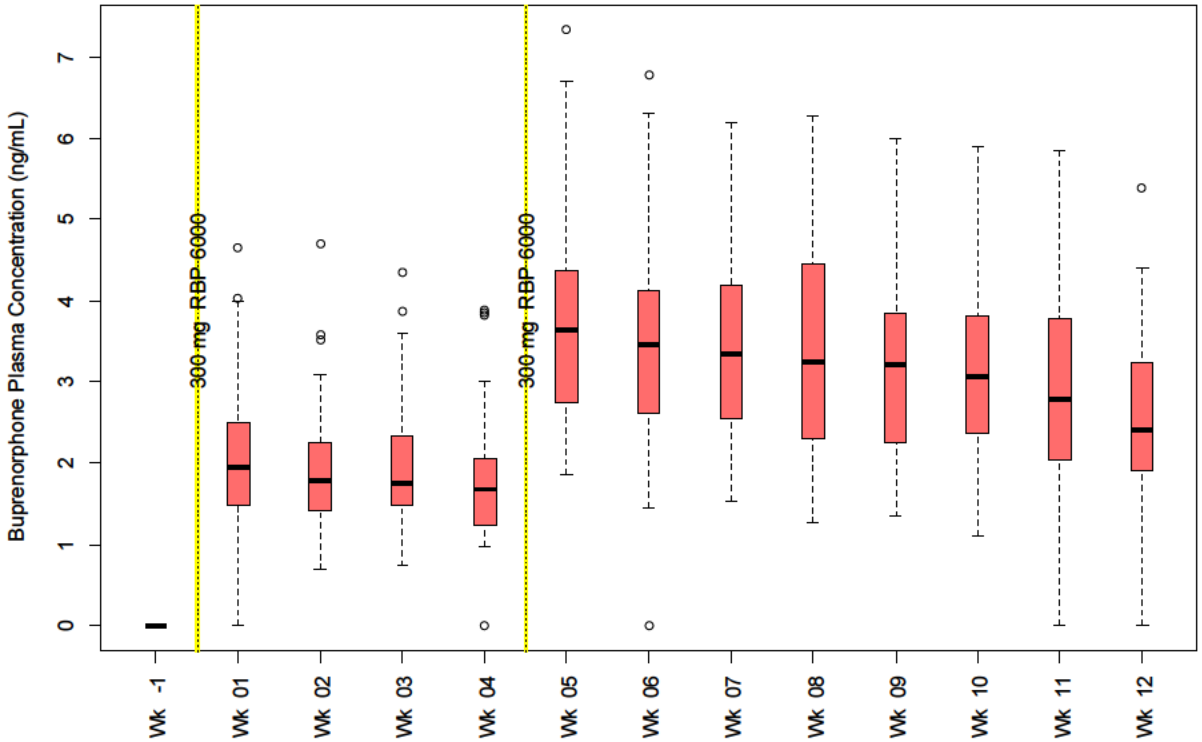
Figure 62: Distribution of Buprenorphine Concentration Measured Immediately Prior to Hydromorphone Session By Hydromorphone Dose Level and by Week



*Vertical yellow lines indicate the timing of SC injections of RBP-6000. The white, pink, and blue boxplots represent the buprenorphine concentration distribution immediately prior to the hydromorphone challenge for 0, 6, and 18 mg, respectively. The 3 hydromorphone sessions are presented in order of increasing hydromorphone dose level for ease of viewing but in the trial the hydromorphone dose sequence was randomized for each patient for each visit.

The figure above demonstrates that hydromorphone administration does not affect buprenorphine exposure, as expected. As such, the data in the figure above were pooled to include all buprenorphine exposures during all 3 hydromorphone test sessions per week.

Figure 63: Distribution of Buprenorphine Concentration Measured Immediately Prior to Hydromorphone Session By Week

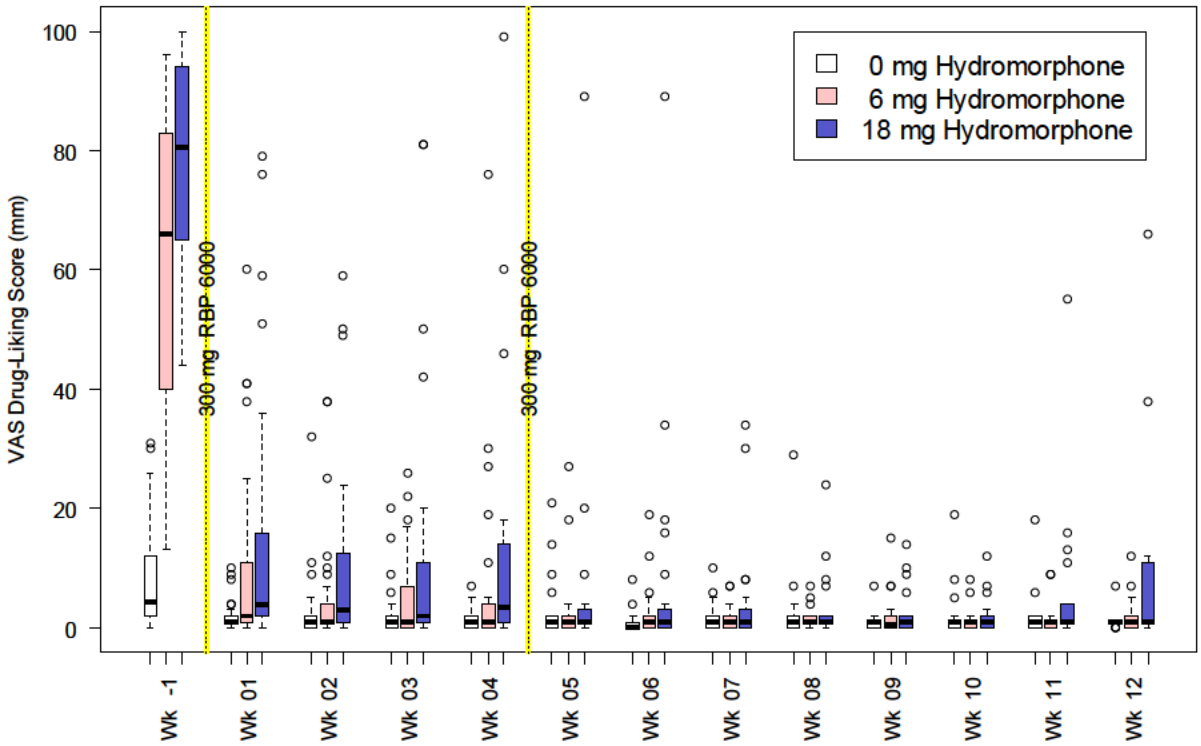


*Vertical yellow lines indicate the timing of SC injections of RBP-6000.

The figure above shows that the buprenorphine exposure decreases over the interval more slowly than would be expected from the PK profile of SL buprenorphine. In addition, there is accumulation following the second dose compared to the first dose. Furthermore, despite the drug being targeted for once monthly administration, the plot above shows that by week 12 (2 months after the last injection), the buprenorphine exposure is still greater than, on average, the exposure after the first injection (Weeks 1-4).

PD measurement was the maximum drug-liking assessment (E_{max}) during each 3-day hydromorphone test session. The drug-liking is assessed using the unipolar Visual Analog Scale (VAS), a 10 cm strip of paper presented to a patient where if patient points to 0 mm this represents minimal liking (neutral response) and if patient points to 100 mm this represents the maximum liking. The plot below shows the distribution of E_{max} drug liking scores.

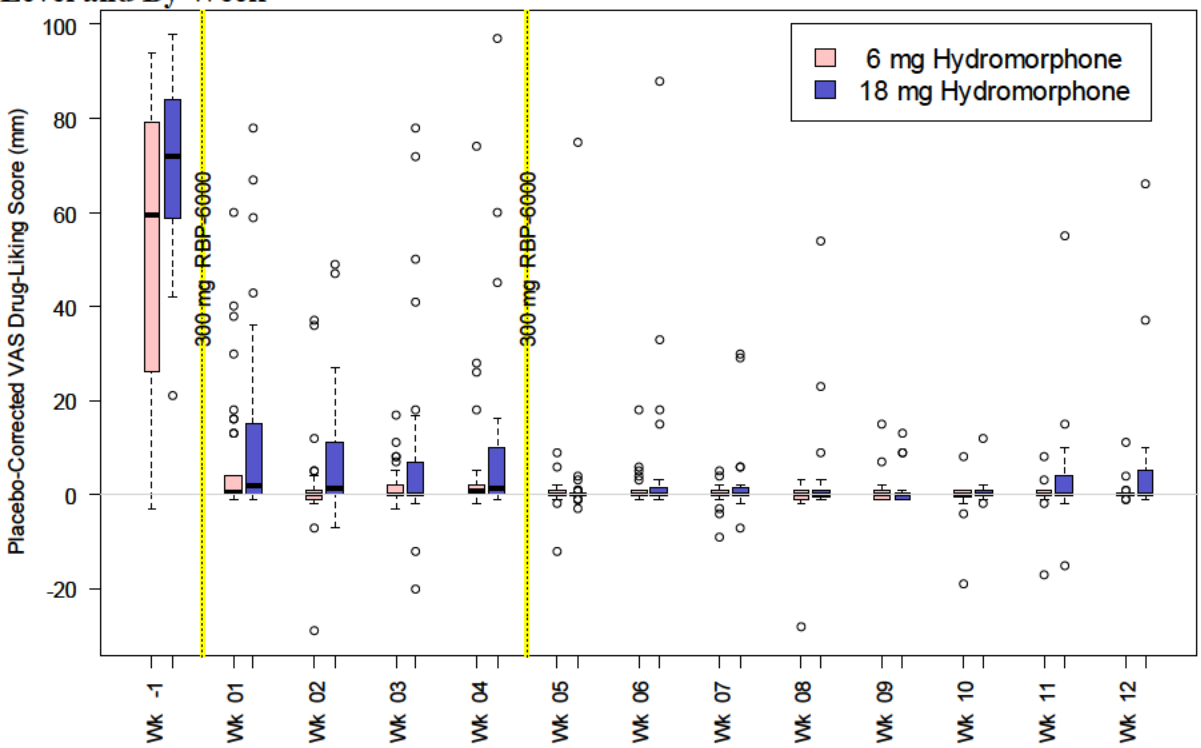
Figure 64: Distribution of Drug-Liking Scores by Hydromorphone Dose Level and by Week



*Vertical yellow lines indicate the timing of SC injections of RBP-6000. The white, pink, and blue boxplots represent the Emax drug-liking score distribution observed during the hydromorphone challenge for 0, 6, and 18 mg, respectively. The 3 hydromorphone sessions are presented in order of increasing hydromorphone dose for ease of viewing but in the trial the hydromorphone dose sequence was randomized for each patient for each visit.

Other than the Week -1 (where drug-liking was assessed in the absence of buprenorphine), the "placebo-response" (drug-liking for the 0 mg hydromorphone session) was effectively zero. As the placebo-response is consistent after RBP-6000 administration, and since the Applicant utilized placebo-corrected E_{max} values for 6 mg and 18 mg hydromorphone, the distribution of placebo-corrected E_{max} scores was also plotted (see figure below).

Figure 65: Distribution of Placebo-Corrected Drug-Liking Scores by Hydromorphone Dose Level and By Week



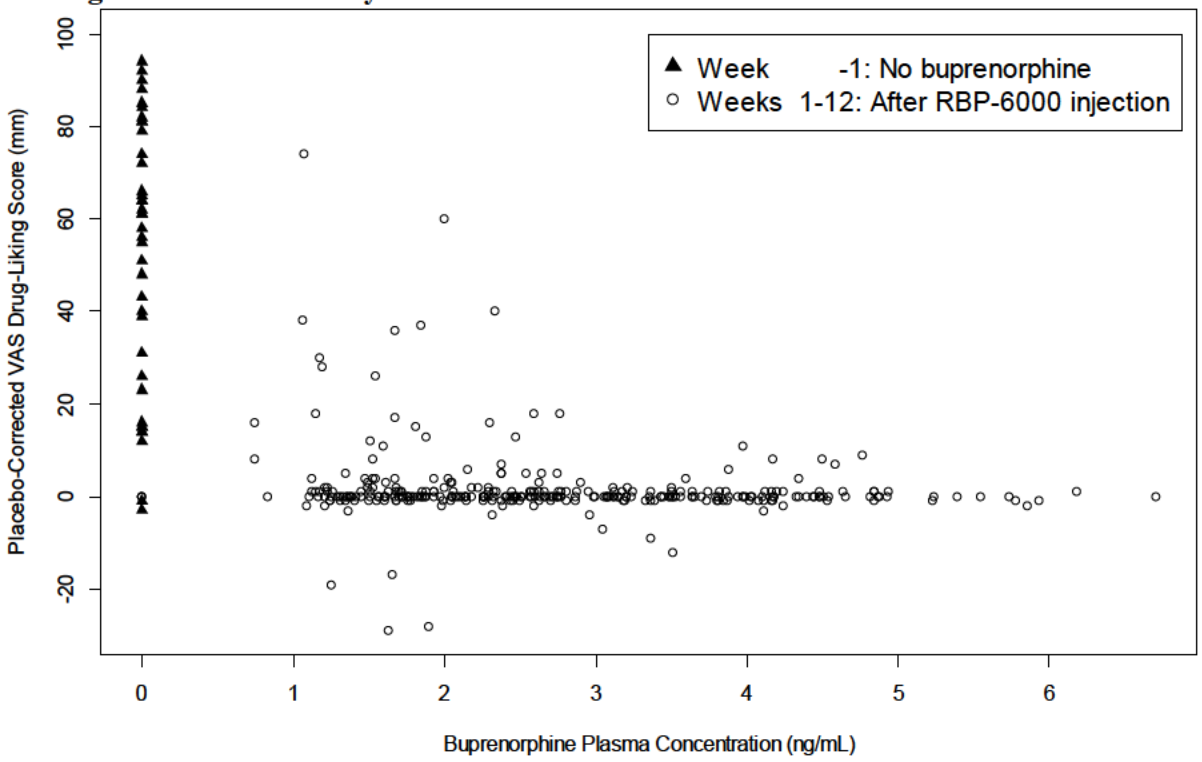
*Vertical yellow lines indicate the timing of SC injections of RBP-6000. The white and blue boxplots represent the placebo-corrected E_{max} drug-liking score distribution observed during the hydromorphone challenge for 6 and 18 mg, respectively. The 2 hydromorphone sessions are presented in order of increasing hydromorphone dose value for ease of viewing but in the trial the hydromorphone dose sequence was randomized for each patient for each visit.

Looking at the figure above, the following observations are apparent:

- *Drug liking is the highest during the qualification period, Week -1, where the hydromorphone challenge was conducted in the absence of buprenorphine*
- *Drug-liking is reduced after RBP-6000 administration (at and after Week 1) compared to drug-liking assessed during baseline or qualification phase, as expected.*
- *RBP-6000 appears to be more effective at reducing the "drug liking" for the 6 mg hydromorphone dose level than for 18 mg, as expected.*
- *The drug-liking scores improve after the 2nd RBP-6000 administration (at and after week 5) compared to scores obtained before the 2nd administration. The improved scores after the 2nd administration are likely due to greater buprenorphine concentrations achieved during this period (which are approximately two times greater after the 2nd injection compared to the period after the first injection, Weeks 1 to 4, as shown in the previous slide).*

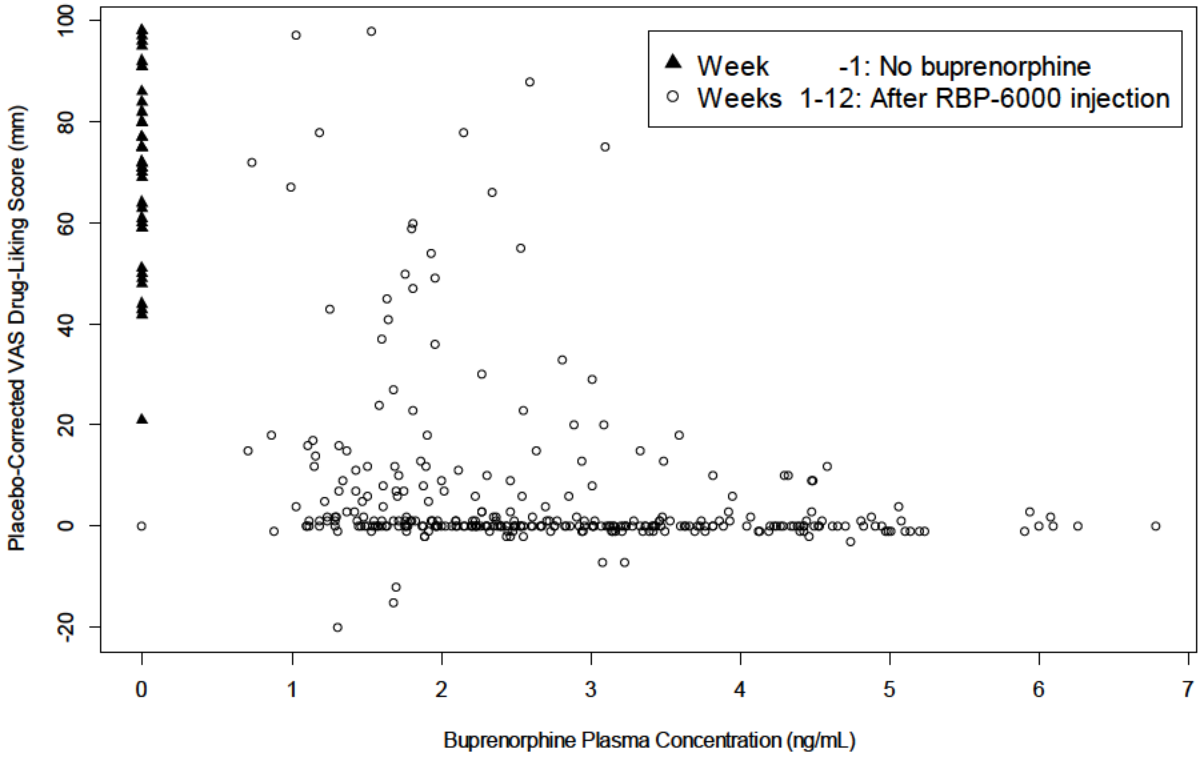
The plots of buprenorphine concentration versus time and placebo-corrected E_{max} versus time show the exposure and "response" independent to one another. A graphical analysis was conducted to explore the relationship between PK and PD. Scatter plots as well as decile plots were generated to assess the relationship between PK and PD (see figures below).

Figure 66: Scatter Plot of Placebo-Corrected Drug-Liking Scores With Corresponding Buprenorphine Concentration for the 6 mg Hydromorphone Dose at Baseline and Throughout 12 Week Study Period



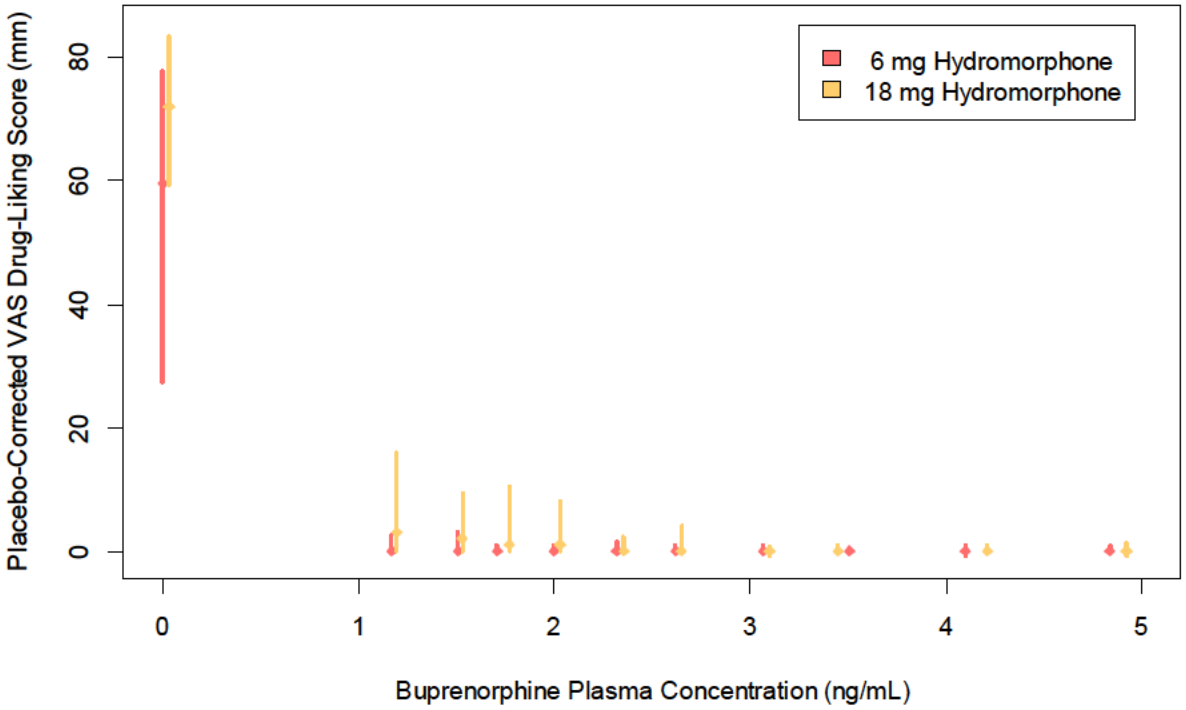
The solid triangle points represent the drug-liking scores observed during week -1 (baseline/qualification period) in the absence of buprenorphine and the circles represent observations acquired after initiating RBP-6000.

Figure 67: Scatter Plot of Placebo-Corrected Drug-Liking Scores With Corresponding Buprenorphine Concentration for the 18 mg Hydromorphone Dose at Baseline and Throughout 12 Week Study Period



The solid triangle points represent the drug-liking scores observed during week -1 (baseline/qualification period) in the absence of buprenorphine and the circles represent observations acquired after initiating RBP-6000.

Figure 68: Quantiles of Placebo-Corrected Drug-Liking Scores With Corresponding Buprenorphine Concentration Deciles for 6 mg and 18 mg Hydromorphone Dose Levels at Baseline and Throughout 12 Week Study Period

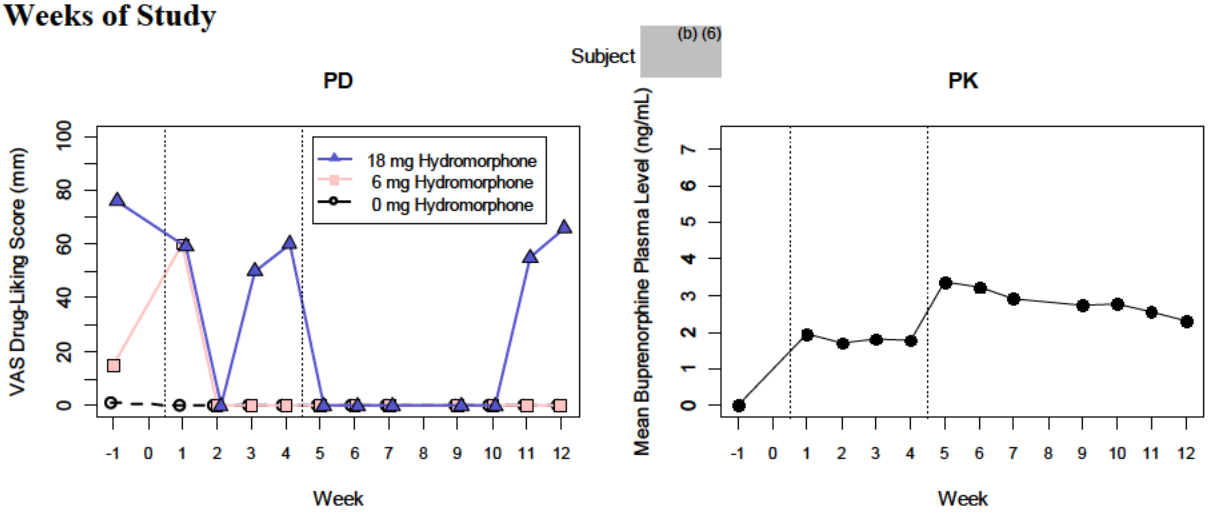


The red and orange bars represent the 25th, 50th, and 75th percentiles of placebo-corrected E_{max} drug liking scores for 6 mg and 18 mg hydromorphone challenge sessions, respectively. Each pair of red and orange bars represents the distribution of placebo-corrected E_{max} drug liking scores at baseline (in absence of buprenorphine) and within the bins of each of 10 buprenorphine concentration deciles.

The plots 66, 67, and 68 demonstrate an apparent central tendency of increasing effectiveness with increasing exposure. However, these plots also demonstrate that the dispersion in drug-liking scores is wider at the lower buprenorphine exposures compared to higher buprenorphine exposures. The dispersion in the drug-liking scores was further investigated to explore and potentially uncover a reason for the wide range of drug-liking scores observed at lower buprenorphine exposures.

When looking at the individual time course of buprenorphine concentration alongside the time course of drug-liking scores, several individuals appeared to presented abrupt changes in the drug-liking scores from week to week. The following plot shows the time-course of PK and PD data for one representative individual (subject (b) (6)), however, approximately one half of the subjects enrolled exhibited this phenomenon.

Figure 69: Representative Individual With Abrupt Changes in Drug-Liking Between Weeks of Study



The left panel shows abrupt changes in the drug-liking score from week-to-week (particularly from week 2-4 and weeks 11-12) for the 18 mg hydromorphone injection which doesn't appear to correlated with the PK profile. The reason for this phenomenon is currently unknown.

Overall, the available PK and PD data provide supportive evidence of opioid blockade. *There is an overall trend of increasing response (that is, reduced drug-liking) with increasing buprenorphine exposure. As expected, higher buprenorphine exposures are required to reduce the drug-liking following an 18 mg hydromorphone challenge compared to a 6 mg hydromorphone challenge.*

However, ***the data demonstrate that in some subjects the drug-liking score can undergo abrupt changes that do not appear to correlate with the PK profile.*** *These observations, such as the PK and PD profiles for individual shown on the previous slide, suggest that****, in addition to buprenorphine concentration, that other factors, factors which are currently unknown, are likely influencing the drug liking scores****.*

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/s/

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