Cross-Discipline Team Leader Review
And
Summary Basis for Approval

Date	November 30, 2017
CDTL	Celia Winchell, M.D.
Division Director	Sharon Hertz, M.D.
NDA/BLA # and Supplement#	209819
Applicant	Indivior, Inc.
Date of Submission	May 30, 2017
PDUFA Goal Date	November 30, 2017
Proprietary Name	Sublocade
Established or Proper Name	(buprenorphine extended release) injection for subcutaneous use
Dosage Form(s)	Injection
Applicant Proposed Indication(s)/Population(s)	Treatment of moderate to severe opioid use disorder (OUD) in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product.
Applicant Proposed Dosing Regimen(s)	Two monthly initial doses of 300 mg followed by either 100 mg or 300 mg monthly maintenance doses.
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	Treatment of moderate-to-severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product followed by dose stabilization for a minimum of 7 days.
Recommended Dosing Regimen(s) (if applicable)	Two monthly initial doses of 300 mg followed by 100 mg monthly maintenance doses.

1 Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
Sublocade (buprenorphine extended release) for subcutaneous injection is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product followed by dose stabilization for a minimum of 7 days. I recommend approval of the application. Opioid use disorder, particularly if classified as moderate or severe, is a serious and life-threatening condition and contributes to increased rates of morbidity and mortality, as well as to social and economic costs to society. Current treatment options include non-drug (behavioral) treatment, as well as medication-assisted treatment (MAT) with antagonists (naltrexone), agonists (methadone) or partial agonists (buprenorphine). Methadone is available only at federally-registered opioid treatment programs (OTPs), and patients must visit the clinic daily for in-person dosing until they meet criteria for receiving gradually-increasing numbers of take-home doses. Methadone has been associated with fatal overdoses in patients and in their household contacts, including children. Oral naltrexone (REVIA) and depot naltrexone (VIVITROL) cannot be initiated until patients are fully detoxified, and may not be suitable or acceptable for all patients. Severe, and potentially serious, precipitated withdrawal can occur when naltrexone treatment is initiated. Serious injection site reactions requiring surgical intervention have been reported with VIVITROL. Oral-transmucosal buprenorphine and buprenorphine/naloxone products and oral naltrexone products are intended to be self-administered by the patient daily. Limitations of daily use products include poor adherence, fluctuating plasma concentrations, intentional “drug holidays,” as well as patient convenience issues. Daily use agonist and partial agonist MAT products are subject to diversion, misuse, abuse, and accidental pediatric exposure. Subdermal implant (PROBUPHINE) is suitable only for patients clinically stable on low-moderate dose of transmucosal buprenorphine (≤ 8 mg buprenorphine), requires surgical insertion and removal, and carries a risk of implant migration (with potentially serious consequences) or expulsion.

SUBLOCADE 300 mg monthly blocks subjective effects of a clinically-relevant dose of opioid agonist after a single dose, and provides even more complete blockade after two monthly doses. The effect of this blockade was shown to translate to clinical efficacy for both a 300 mg/month regimen, and a regimen of 100 mg/month after an initial 2-month loading phase with 300 mg/month, as demonstrated by statistically significant superiority over placebo in the cumulative distribution of negative opioid use assessments as well as an analysis of responders.

Taken together, and considering the established efficacy of Subutex, these studies provide substantial evidence of efficacy for SUBLOCADE in the treatment of moderate or severe OUD in patients initially briefly treated with transmucosal buprenorphine.

No direct head-to-head comparison to existing treatment was included in the application, but Sublocade has the potential to yield improved efficacy through improved adherence. It offers clear advantages over other agonist and partial agonist treatments of OUD that are dosed on a daily basis, in that no take-home supplies are needed. This is expected to reduce the potential for misuse, abuse, diversion, and accidental overdose.

The safety profile of buprenorphine is well-characterized, and the Sublocade safety profile appears similar, despite higher plasma exposures. The size of the safety database was appropriate to characterize the safety. Dose-dependent adverse effects were consistent with buprenorphine's known safety profile (hepatic enzyme elevations, GI symptoms); additionally, injection site reactions were more common with the higher dose, potentially due to greater volume. The labeling will recommend that the 300 mg/month regimen be reserved for those who do not respond to the 100 mg/month (after two months of 300 mg/month loading dose). To further elucidate when the benefit of the 300 mg/month regimen outweighs the risk, post-marketing studies to determine which populations might benefit from the higher-dose regimen, and to determine a process for transitioning patients with long-term stability on a transmucosal buprenorphine dose to a monthly dose of Sublocade without the use of a loading dose, are proposed.

Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated in a patient still dependent on a full agonist. Additionally, there may be circumstances under which the rapid discontinuation or dose reduction of buprenorphine might be

desirable for a given patient. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with SUBLOCADE for a period of time. There are limited possibilities for surgical removal. Patients developing intolerance to buprenorphine will require long-term monitoring by a health care professional.

Moderate-to-severe opioid use disorder is a serious and life-threatening condition and the need for more treatment options and greater access to treatment is clear. Sublocade, as a HCP-administered long-acting depot providing a sustained effective plasma level of buprenorphine over a prolonged period, has the potential to address some of the limitations of available options.

The identified safety concerns are outweighed by the potential benefit and can be managed with the proposed labeling, REMS, and post-marketing activities. The labeling will limit the use of Sublocade to patients who have been dose-stabilized on transmucosal buprenorphine for at least 7 days to mitigate the risk of precipitated withdrawal. Post-marketing studies to evaluate whether Sublocade can be administered without initial dose run-in on transmucosal buprenorphine will be required. The labeling will alert prescribers to the long persistence of buprenorphine plasma levels after Sublocade treatment, and a MedGuide (not part of the REMS) will provide this information to patients.

Postmarketing activities will also include studies to assess which patients would benefit from the higher dosing regimen; to assess the feasibility of administering Sublocade at longer inter-dose intervals; and to determine a process for transitioning patients with long-term stability on a transmucosal buprenorphine dose to a monthly dose of Sublocade without the use of a loading dose. Enhanced pharmacovigilance focused on intravenous administration of Sublocade, and on surgical removal of the Sublocade depot will also be required.

A REMS to ensure that the product will be administered by HCPs and not distributed to patients will be required to mitigate the risk of intravenous injection. The goal of the REMS is to mitigate the risk of serious harm or death with intravenous self-administration by ensuring healthcare settings and pharmacies are certified and only dispense Sublocade directly to a health care provider for administration by a healthcare provider.

The following materials are part of the Sublocade REMS**:**

1. Healthcare Setting and Pharmacy Enrollment Form

2. Dear Healthcare Provider REMS Letter
3. Fact Sheet
4. REMS Program Website

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Opioid use disorder or OUD, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is a chronic, relapsing disease characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and physical consequences. Moderate to severe OUD corresponds, roughly, to the DSM-IV diagnosis "opioid dependence," and to the widely-used term, "addiction." Mild OUD corresponds to the DSM-IV diagnosis "opioid abuse." - In 2016, the National Survey on Drug Use and Health determined that over 2.1 million Americans aged 12 and over met criteria for either opioid abuse or dependence. - In 2015, the CDC reported that drug overdose was the leading cause of accidental death in the US, with 52,404 lethal drug overdoses in 2015. Of these, 20,101 overdose deaths were related to prescription pain relievers, and 12,990 overdose deaths were related to heroin. - Goals of treatment vary for individual patients, but typically involves a substantial change in illicit drug use behavior sufficient to translate to clinical benefit. - For many patients, discontinuation of treatment leads to relapse; therefore, treatment may be required chronically.	Opioid use disorder, particularly if classified as moderate or severe, is a serious and life-threatening condition and contributes to increased rates of morbidity and mortality, as well as to social and economic costs to society.
Current Treatment Options	- Current treatment options include non-drug (behavioral) treatment, as well as medication-assisted treatment (MAT) with antagonists (naltrexone), agonists (methadone) or partial agonists (buprenorphine). o Behavioral treatment alone (individual or group counseling, self-help groups) is not effective for many patients. o Methadone is available only at federally-registered opioid treatment programs (OTPs), and patients must visit the clinic daily for in-person dosing until they meet criteria for receiving	Buprenorphine monthly depot injection would be a desirable addition to the therapeutic armamentarium. - Convenience of monthly vs daily dosing - Provides consistent buprenorphine levels sufficient to block effects of exogenous opioids - Improves adherence

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	gradually-increasing numbers of take-home doses. Methadone has been associated with fatal overdoses in patients and in their household contacts, including children. o Subdermal implant (PROBUPHINE) is suitable only for patients clinically stable on low-moderate dose of transmucosal buprenorphine (≤ 8 mg buprenorphine), requires surgical insertion and removal, and carries a risk of implant migration (with potentially serious consequences) or expulsion. o Oral naltrexone (REVIA) and depot naltrexone (VIVITROL) cannot be initiated until patients are fully detoxified, and may not be suitable or acceptable for all patients. Severe, and potentially serious, precipitated withdrawal can occur when naltrexone treatment is initiated. Serious injection site reactions requiring surgical intervention have been reported with VIVITROL. o Oral-transmucosal buprenorphine and buprenorphine/naloxone products and oral naltrexone products are intended to be self-administered by the patient daily ▪ Limitations of daily use products include poor adherence, fluctuating plasma concentrations, intentional "drug holidays," as well as patient convenience issues. ▪ Daily use agonist and partial agonist MAT products are subject to diversion, misuse, abuse and accidental pediatric exposure	- Reduces potential for diversion, misuse, abuse and accidental pediatric exposure - No surgical procedure needed - No rescue buprenorphine needed
Benefit	- The opioid blockade study, Study 13-0002, NCT02044094, demonstrated that after SUBLOCADE injections at Weeks 1 and 4, on average, subjective effects of both 6 mg and 18 mg doses of hydromorphone were blocked in 39 non-treatment-seeking subjects with OUD, although significant variation was seen across subjects. Complete blockade continued throughout the 8 weeks of observation that followed the 2nd SUBLOCADE injection. Conversely, stabilization doses of SL buprenorphine in Wk 0 failed to provide full blockade of subjective effects hydromorphone 18 mg i.m. - Dose-response analysis showed a decreasing number of outliers (unblocked responses) with increasing plasma levels, with very few outliers above a plasma level of 3 ng/ml. - The pivotal efficacy trial, Study 13-0001, NCT02357901 (N=504) demonstrated that patients treated with SUBLOCADE (dosing regimens 300 mg/month x 6 months or 300 mg/month x 2 months followed by 100 mg/month x 4 months) had superior treatment response compared to	SUBLOCADE 300 mg monthly blocks subjective effects of a clinically-relevant dose of opioid agonist after a single dose, and provides even more complete blockade after two monthly doses. The effect of this blockade was shown to translate to clinical efficacy for both a 300 mg/month regimen, and a regimen of 100 mg/month after an initial 2-month loading phase with 300 mg/month, as demonstrated by statistically significant superiority over placebo in the cumulative distribution of negative opioid use assessments as well as an analysis of responders.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients treated with placebo. Both the pre-specified responder definition (80% of weekly drug use assessments negative between weeks 5-24) and the cumulative distribution of % negative assessments were clearly superior to placebo for both treatment regimens, although the two regimens did not differ. - Moreover, 13% of patients in the 300/300 mg group and 12% of patients in the 300/100 mg group achieved 100% negative drug use assessments over the 20-week efficacy ascertainment period, vs only 1% of patients in the placebo group. - Effects of this magnitude in drug-use patterns are considered a clinical relevant surrogate endpoint and have been used previously by the division as a basis for approval of Vivitrol - Quality of both studies was adequate and the study population is an adequate representation of the treatment population with OUD in the USA; however, the efficacy trial population was somewhat enriched for buprenorphine responders by virtue of an initial open-label run-in period. Somewhat lower response rates may be seen in a less selected population. - There is some indication that certain sub-populations might benefit from the higher dose regimen, but the findings are not conclusive are require further exploration. - Sublocade is administered by a health care provider subcutaneously every month and provides advantages over daily dose MAT products in terms of patient adherence, patient convenience, and risks of abuse, misuse, and accidental exposure.	Taken together, and considering the established efficacy of Subutex, these studies provide substantial evidence of efficacy for SUBLOCADE in the treatment of moderate or severe OUD in patients initially briefly treated with transmucosal buprenorphine. However, no incremental benefit of the higher dose regimen was noted in the overall population.
Risk and Risk Management	- The active ingredient, buprenorphine, has been marketed since 1981 and has been approved for opioid dependence treatment since 2002. The systemic safety profile of SUBLOCADE is consistent with the established safety profiles of transmucosal buprenorphine products used for treatment of OUD. - Safety concerns related to buprenorphine include hepatic effects, cardiac conduction effects, allergy/anaphylaxis, and general effects of the opioid class (e.g. respiratory depression, CNS depression, etc.) - In a safety database of 848 opioid-dependent subjects, systemic effects of buprenorphine associated with SUBLOCADE (≥ 2% occurrence) included headache, nausea, constipation, vomiting. elevated liver	The safety profile of buprenorphine is well-characterized, and the Sublocade safety profile appears similar, despite higher plasma exposures. The size of the safety database was appropriate to characterize the safety. Dose-dependent adverse effects were consistent with buprenorphine's known safety profile (hepatic enzyme elevations, GI symptoms); additionally, injection site reactions were more common with the

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	enzymes, sedation and somnolence - Common injection site reactions included injection site pain, pruritus and erythema; no ISRs were serious. - Treatment-emergent adverse events leading to drug discontinuation were reported in ≤5% of subjects in all treatment groups - TEAEs leading drug dose reductions were reported in 7.3% of subjects receiving RBP-6000 in Phase 3 OL study - No Hy's law case was identified in the clinical development program - One death occurred in RBP-6000 300/300 mg group due to homicide - A total of 50 non-fatal SAEs occurred among 42 subjects in Phase 3 studies and were generally not drug-related - Increase from baseline QTc of greater than 60 msec at any time was noted in 1% of the 300 mg/100 mg group vs 2% of the 300 mg/300 mg group, and one patient in the 300 mg/300 mg group was found to have a QTc greater than 500 msec. QTc findings were sporadic and transient and none led to aberrant ventricular rhythm. - Dose-dependent AE findings included: o TEAEs leading to drug discontinuation more common in the SUBLOCADE 300/300 mg group (5%) vs SUBLOCADE 300/100 mg group (3.5%) o ISRs more common in the SUBLOCADE 300/300 mg group (18.9 %) vs SUBLOCADE 300/100 mg group (13.8%) o LFT elevations (≥ 3x ULN (post-baseline)) more common in SUBLOCADE 300/300 mg group (ALT 12.4%, AST 11.4%) than SUBLOCADE 300/100 mg group (ALT 5.4%, AST 7.9) - Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with SUBLOCADE for a period of time. There are limited possibilities for surgical removal. Patients developing intolerance to buprenorphine effects will require long-term monitoring by a health care professional. - Buprenorphine itself can precipitate withdrawal if initiated in patients who are not yet in significant opioid withdrawal. For this reason, initial dosing is generally cautious and typically begins with a dose of 2 mg- 4 mg. Sublocade contains a high dose of buprenorphine. The clinical trials included a significant period of dose run-in on transmucosal buprenorphine. It is not known whether Sublocade could precipitate withdrawal if initiated in patients who have not had a period of transmucosal buprenorphine treatment. Clinicians may be interested in initiating Sublocade expeditiously, for example, in patients recently revived from an overdose. It is not known if this can be accomplished safely. - SUBLOCADE forms a solid if injected into blood (in vitro). If patients	higher dose, potentially due to greater volume. Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated in a patient still dependent on a full agonist. Additionally, there may be circumstances under which the rapid discontinuation or dose reduction of buprenorphine might be desirable for a given patient. Rapid reduction of plasma levels of buprenorphine is not possible in patients who have been treated with SUBLOCADE for a period of time. There are limited possibilities for surgical removal. Patients developing intolerance to buprenorphine effects will require long-term monitoring by a health care professional. The labeling will limit the use of Sublocade to patients who have been dose-stabilized on transmucosal buprenorphine for at least 7 days to mitigate the risk of precipitated withdrawal, and will recommend that the 300 mg/month dose be reserved for those not responding to the 100 mg/month dose. The labeling will alert prescribers to the long persistence of buprenorphine plasma levels after Sublocade treatment, and a MedGuide (not part of the REMS) will provide this information to patients. Post-marketing studies to evaluate whether Sublocade can be administered

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	obtain direct access to the product, there is a risk they may choose to attempt to inject the product intravenously. Notably, the consequences of intravenous injection of the contents of the pre-filled syringe are not known, but based on in vitro evaluation, it is anticipated that there is a risk of occlusion, tissue damage, and emboli.	without initial dose run-in on transmucosal buprenorphine will be required; to assess which patients would benefit from the higher dosing regimen; to assess the feasibility of administering Sublocade at longer inter-dose intervals; and to determine a process for transitioning patients with long-term stability on a transmucosal buprenorphine dose to a monthly dose of Sublocade without the use of a loading dose. Enhanced pharmacovigilance focused on intravenous administration of Sublocade, and on surgical removal of the Sublocade depot will also be required. A REMS is required to ensure that SUBLOCADE is not distributed directly to patients, and is administered by a health care professional, to mitigate the risk of serious consequences should the product by administered intravenously.

2 Introduction

Sublocade (buprenorphine extended-release injection, also known as RBP-6000[1]) is a drug-device combination product with 18% (weight/weight) buprenorphine base in the ATRIGEL Delivery System in a prefilled syringe. Upon SC injection, Sublocade forms a semi-solid depot that releases buprenorphine via diffusion as the ATRIGEL polymer biodegrades. Sublocade provides sustained plasma levels of buprenorphine sufficient to block the effects of exogenous opioids over a minimum of 28 days and is intended for the treatment of moderate to severe opioid use disorder (OUD) in patients who have undergone treatment initiation and dose-stabilization with a transmucosal buprenorphine-containing product. The product should be used as part of a complete treatment plan to include counselling and psychosocial support.

Because of the potential for a depot product to mitigate risks of abuse, diversion, and accidental pediatric exposure associated with oral transmucosal buprenorphine, the application was granted a priority review.

Although buprenorphine products have been approved for the treatment of opioid dependence, there have been no monthly depot formulations previously approved. To ensure that the amount of buprenorphine provided and the proposed dosing interval were suitable to support the proposed indication, the Applicant was required to support a finding of efficacy for this product with two adequate and well-controlled clinical trials or one adequate and well-controlled clinical trial and a human behavioral pharmacology study demonstrating the ability of the product to block the effects of exogenous opioids (blockade study). In this submission, the Applicant has provided efficacy data from a blockade study, and from a single, double-blind, placebo-controlled trial in patients newly-entering buprenorphine treatment demonstrating that the blockade effect translates to an effect on illicit drug use. Additionally, safety experience from an open-label trial and from the Phase 1 program was provided.

The Applicant's submission included safety data from 1083 subjects who were treated with Sublocade in clinical trials and clinical pharmacology studies. The Sponsor tabulates that 542 patients were exposed for 24 weeks or longer and 320 patients were exposed for 48 weeks or longer.

Particular attention was given to the safety experience with the 300 mg/month dosing regimen because the steady-state exposure greatly exceeds that associated with the maximum recommended dose of Subutex, 24 mg/day. Labeled risks of oral transmucosal buprenorphine for opioid dependence include hepatic effects, possible effects on cardiac conduction, and allergic reactions, as well as the possibility of overdose particularly when combined with other depressants. The overall safety experience with Sublocade is consistent with the known safety profile of buprenorphine.

[1] Terms are used interchangeably in this review.

One risk associated with Sublocade that differentiates it from the transmucosal formulations is the concern that serious consequences could ensue if the product were injected intravenously. A Risk Mitigation and Evaluation Strategy (REMS) is proposed to ensure that the product is administered appropriately.

3 Background

Buprenorphine is a partial agonist at the μ-opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence[2]. Three other transmucosal formulations and a six-month, surgically-placed implant have subsequently been approved for opioid dependence, as well as two transdermal products and one transmucosal product for pain. Approximately 12.2 million prescriptions from outpatient retail pharmacies were dispensed and approximately 1.6 million patients received a dispensed prescription for buprenorphine tablets or film during 2016. Primary care physicians accounted for 39% of dispensed prescriptions, followed by psychiatrists (21%), osteopaths (14%), emergency physicians (4%) and anesthesiologists (4%). Recently, the authority to prescribe buprenorphine for office-based treatment of OUD was expanded to include Nurse Practitioners and Physician's Assistants, so the distribution of specialties may be expected to change in the future.

Buprenorphine was developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the μ-opioid receptor. First, buprenorphine had been shown to have a ceiling effect for respiratory depression, suggesting that it would be "impossible to overdose" on buprenorphine. Second, initial clinical evaluations of buprenorphine's ability to produce physical dependence led to the conclusion that physical dependence to buprenorphine, if it developed, was associated with a mild withdrawal syndrome. Third, it was expected to have limited attractiveness as a drug of abuse relative to full agonists.[3]

Buprenorphine was expected to have limited abuse potential for two reasons. First, due to its partial agonist properties, the euphorigenic effects of buprenorphine were understood to reach a "ceiling" at moderate doses, beyond which increasing doses of the drug do not produce the increased effect that would result from full opioid agonists. Second, when a partial agonist displaces a full agonist at the receptor, the relative reduction in receptor activation can produce withdrawal effects. Individuals dependent on full agonists may therefore experience sudden and severe symptoms of withdrawal if they use buprenorphine. These features were expected to limit its attractiveness as a drug of abuse for patients and for illicit use.

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[2] Subutex, buprenorphine sublingual tablets (Reckitt Benckiser (now Indivior) NDA 20732) and Suboxone, buprenorphine/naloxone sublingual tablets (Reckitt Benckiser (now Indivior) NDA 20733). Naloxone is intended to further deter abuse by the intravenous route by precipitating withdrawal if the product is injected by persons dependent on full agonists.

[3] Many of these beliefs have subsequently been found to have been erroneous, or at least overstated, but these were the generally-held views about buprenorphine's pharmacology at the time it was being developed.

In addition to the improved safety profile, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, deterring abuse of opioids by buprenorphine-maintained patients.

Unfortunately, despite these features, buprenorphine sublingual products have been increasingly identified in the illicit drug market, and it is known that they are diverted, abused, and misused. Additionally, they have been implicated in a number of cases of accidental poisonings of small children. Therefore, a depot injection which would be difficult to divert or abuse, and would be less likely to be accidentally ingested by small children, offers potential advantages. In addition, if a depot or implantable product provided a sufficient plasma level of buprenorphine to block the effects of exogenous opioids, the nature of the product would enforce compliance so that patients could not periodically discontinue use to allow the blocking effect to dissipate in order to experience the effects of their opioids of choice.

Comparison of exposures after Sublocade's 100 mg/month and 300 mg/month doses to sublingual buprenorphine demonstrate that, at steady-state (4th injection), both doses deliver plasma concentrations ($C_{avg,ss}$) that are comparable to, or higher than, doses in the therapeutic range for Subutex. (See Table 2 Comparison of buprenorphine mean pharmacokinetic parameters between Subutex and SUBLOCADE, page 24, and Table 3 Pharmacokinetic Parameters of Phase 3 Dosing Regimens, page 25.)

3.1 Clinical Development of Sublocade

The clinical development of Sublocade was undertaken with advice from the Division. At pre-IND and advice meetings, options for populations (e.g., new entrants to treatment vs. established, stable patients) were discussed, along with the type and number of studies needed to support approval. Indivior elected to study patients new to treatment, and we agreed that this claim could be supported by a study showing that the product yielded a plasma level sufficient to completely block (not just attenuate) the effects of a clinically-relevant dose of an opioid agonist, taken together with a controlled study demonstrating that the blockade effect translated to a clinically-relevant change in drug-use behavior over a six-month treatment period.

The blockade of subjective response to opioids is one of the ways in which buprenorphine treatment exerts its effect, through the behavioral principle of extinction. When a behavior is not reinforced, it is less likely to occur. Illicit opioid use is reinforced by the subjective effects of the drug. Blockade is particularly important early in treatment when a "slip" (isolated incident of illicit use) could turn into a "relapse" (return to out-of-control use). By preventing the reinforcing effects of the "slip," a treatment that provides a blockade effect can help the patient discontinue the drug self-administration behavior. Some stable patients or highly-motivated patients may not require the blockade effect for effective treatment long-term.

As recommended, Indivior undertook appropriate studies to identify the target plasma exposure for a blocking effect, demonstrated the extent and duration of opioid blockade were appropriate for the planned dosing interval, and used this information to design their controlled clinical efficacy trial. Although the Application rests in part on cross-referenced data on the efficacy of Subutex, the nature of the product is sufficiently different from Subutex that two studies were

needed to support approval. The blockade study was accepted in lieu of a second efficacy study. Both the blockade study and the controlled efficacy trial are considered necessary for approval.

3.1.1 Background Related to Efficacy Endpoints and Study Design

There is currently no standard approach to clinical trials in this therapeutic area.

Previously-approved products were supported by a variety of studies with treatment as long as 40 weeks, and various analytic approaches were applied in evaluating the results. All focused the assessment of efficacy on the patterns of on-treatment drug use, primarily through frequent collection of urine toxicology samples.

Drug use patterns are a convenient surrogate, but many patients, families, and clinicians may be interested in study designs that establish whether a treatment has an impact on other aspects of opioid use disorder and its effects on how patients feel, function, or survive. Historically, direct clinical measures have always been welcome, but prove challenging to incorporate into clinical trials. For example, although mortality and viral seroconversion are outcomes of interest, both occur at very low rates in clinical trials and would require much larger sample sizes to detect an effect than studies with drug use patterns as the primary endpoint. A patient-reported outcome assessment could be developed using appropriate methods, with input from patients and family members to determine the most concerning symptoms/experiences associated with OUD, but such an instrument does not currently exist. Retention in treatment, *per se*, is not recommended as a stand-alone endpoint. Many features of study design can produce incentives to remain "in treatment" without accruing significant clinical improvement.

For lack of available direct clinical measures, analysis of the pattern of drug use remains the primary approach to assessing treatment response. The Division has taken the position that analyses focused on group means (such as mean percent negative urine tests), which have been used in some prior studies, are not the most clinically meaningful approach because they do not reflect the experience of individual patients, who might range from complete responders to complete non-responders. In discussing how individual response should be assessed, there has been considerable debate over whether endpoints focused on patients attaining complete abstinence from illicit drug use are realistic, and whether they are necessary to ensure that the drug yields clinical benefit. As described below, the responder definition used in this study is not an "abstinence" endpoint.

Several features were incorporated into this program to address the difficulties of retaining patients in treatment and to address the concern that patients may be clinically successful despite occasional illicit drug use episodes. These include:

- Less frequent urine toxicology tests

  Historically, studies of opioid dependence treatment have incorporated thrice-weekly urine sampling. This frequency was identified as providing the best balance between detecting all use and avoiding false-positive tests due to "carry-over" positives, based on the time window of detection for heroin, which was the most commonly-used opioid in populations being studied when this approach was established. Additionally, this approach was not considered unduly burdensome because the treatments being evaluated were agonists that were administered in-clinic on a daily basis.

In studies of treatments that are not administered under supervision daily, or treatments that are not inherently reinforcing, it has been challenging to ensure complete collection of thrice-weekly samples. There has been concern that a study design with frequent sampling, along with an analytic strategy of imputing positive results to missing samples, creates an unrealistic situation in which even some clinically successful patients would be adjudicated as unsuccessful.

Indivior's clinical studies employed weekly, *scheduled*, urine testing. It is understood that weekly sampling may miss some occasions of use, and that scheduled testing may allow patients to deliberately avoid detection of use through timing their episodes of drug use. Thus, even if the definition of response is 100% negative samples, patients who are continue to have some episodes of use may be adjudicated as successful, because some use will not be detected. We accept this for reasons of feasibility.

- A responder definition that allows a few missing or positive samples

  The use of a responder definition that does not require all samples to be present and negative, particularly during a study with an infrequent sampling schedule introduces additional flexibility. The number or percent of allowable missing or positive samples was chosen taking into consideration the total number of samples to be collected. For example, "80% of samples negative" would be more compelling in a six-month study with thrice-weekly samples (58 negative samples) than in a study with once-monthly samples (4 negative samples). Indivior's studies employed weekly testing.

- The incorporation of a "grace period" (assessments at the beginning of treatment which are not considered in the analysis) because patients may not respond immediately. Indivior's studies considered the first four weeks to be a grace period.

- The use of a "continuous responder" analysis.

  One approach that the Division has proposed is to perform an analysis that considers the full range of responder definitions, from use detected at zero visits to use detected at all visits, but to emphasize the effect of the drug on promoting a higher proportion of negative assessments. This approach, the continuous responder curve, or the cumulative distribution function (CDF) of drug use assessments, was employed in this program. The continuous responder curve gives an overall picture of the drug's effect on drug use behavior. Augmenting this analysis with a responder rate comparison ensures that the effect is of a magnitude that has clinical meaningfulness.

In Indivior's study, there are weekly, scheduled, samples collected over 24 weeks. However, the first month is considered a "grace period" because patients may not respond immediately. A CDF of patient responses was the primary endpoint, and the secondary endpoint was a responder analysis. The responder definition agreed to was 80% negative. This was simply a pragmatic choice. A responder is defined as a patient who provides self-report and laboratory evidence of absence of illicit opioid use on 16 of 20 *scheduled* weekly visits. Such patients may have a number of undetected occasions drug use; however the ability to attend study visits and provide

negative urine samples over a 24-week period is nevertheless an indicator of some degree of clinical stability.

There is also no standard approach to studies intended to demonstrate that a product can block the effects of exogenously-administered opioids. The ability of buprenorphine to attenuate the reinforcing effects of other opioids has been studied in various ways over the past decades, but at the time this development program was initiated, studies in the literature did not support a consistent conclusion about the relationship between plasma buprenorphine levels, opioid receptor occupancy, and blockade of clinically relevant doses of opioids of abuse. Heterogeneity in the challenge doses used, the interpretation of the term "blockade" (to mean either any detectable attenuation of agonist effect, or complete prevention of agonist effect), and in the doses, route, and timing of the buprenorphine administration complicated interpretation of literature findings, however, the Division's review of the literature suggested that clinically-relevant doses of opioids of abuse may require fairly high doses of buprenorphine (and by extension, plasma levels) for full blockade, and that 85% receptor occupancy or better would be a reasonable target, to allow room for inter-individual variation, given that the shape of the curve relating plasma level to receptor occupancy in published studies at that time was exponential. Our recommendation was to target exposure of approximately 3 ng/ml, and to establish in a behavioral pharmacology trial that the selected dose was capable of blocking the reinforcing effects of a clinically-relevant dose of a full agonist.

The design of the blockade study was based on designs used to evaluate human abuse liability, and was developed with input from the Controlled Substances Staff and supporting biostatistical reviewers. A broadly similar design was used to support approval of Vivitrol (depot naltrexone, Alkermes NDA 21-897) for treatment of opioid dependence.

3.2 Safety Concerns Related to Formulation

After injection of SUBLOCADE, contact between aqueous biological fluids and the polymer matrix result in precipitation of the PLGH, leaving a biodegradable solid depot at the site of injection. Because individuals with OUD are known to use a variety of opioids by unintended routes, sometimes with severe consequences, Indivior performed an *in vitro* study to simulate the effects of injecting Sublocade intravenously, by adding the product to a sample of dog blood. Immediate clogging was observed (Report (b) (4)). Based on this result, Indivior and the Division agreed that it was likely that, should the product be injected intravenously, an occlusion would form due to rapid solidification of the formulation when placed in aqueous fluid. This raised a safety concern about the possible consequences of this type of misuse, which could involve occlusion, tissue damage, or possibly embolus.

3.3 Legal and Regulatory Issues Constraining Buprenorphine Treatment

Buprenorphine is a Schedule III Controlled Substance and physicians prescribing Probuphine must comply with the relevant aspects of the Controlled Substances Act. In addition, the provision of agonist treatment of opioid addiction is governed by certain legal requirements. Unlike methadone, buprenorphine may be prescribed by physicians meeting certain requirements.

Methadone treatment of opioid addiction is delivered in a closed distribution system (opioid treatment programs, OTPs) that originally required special licensing by both Federal and State authorities, under the Narcotic Addict Treatment Act of 1974. The current regulatory system is accreditation-based, but OTPs must still comply with specific regulations that pertain to the way clinics are run, the credentials of staff, and the delivery of care. To receive methadone maintenance, patients are required to attend an OTP, usually on a daily basis, with the possibility of earning the privilege of taking home doses as their treatment stability increases. Buprenorphine may also be administered to patients at OTPs.

Buprenorphine treatment is covered in Title XXXV of the Children's Health Act of 2000 (P.L. 106-310), which provides a "Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment of Opioid-Dependent Patients." This part of the law is known as the Drug Addiction Treatment Act of 2000 (DATA 2000). Under the provisions of DATA 2000, qualifying physicians may obtain a waiver from the special registration requirements in the Narcotic Addict Treatment Act of 1974, and its enabling regulations, to treat opioid addiction with Schedule III, IV, and V opioid medications that have been specifically approved by FDA for that indication, and to prescribe and/or dispense these medications in treatment settings other than licensed OTPs, including in office-based settings. The Comprehensive Addiction and Recovery Act (CARA) of 2016 (P.L. 114-198) extended the privilege of prescribing buprenorphine in office-based settings to qualifying nurse practitioners (NPs) and physician assistants (PAs) until Oct. 1, 2021. At present, the only products covered by DATA 2000 (i.e., Schedule III-IV, approved for the indication) are buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and films.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to necessary, concurrent psychosocial services. The 8 hour training courses are provided by various physician organizations (e.g. APA) and delivered in-person, in web-based formats, or through other mechanisms. Physicians who obtain DATA 2000 waivers may treat opioid addiction with products covered by the law in any appropriate clinical settings in which they are credentialed to practice medicine. Specific requirements for non-physician HCPs are stipulated in the CARA legislation. Under the DATA 2000, the number of patients a provider may treat with buprenorphine is capped at an "applicable number," initially 30 and then increasing as the provider gains experience. The text of the legislation also notes that "The Secretary may exclude from the applicable number patients to whom such drugs or combinations of drugs are directly administered by the qualifying practitioner in the office setting." This implies that the Secretary could determine that the number of patients a given provider may treat with Sublocade is not limited.

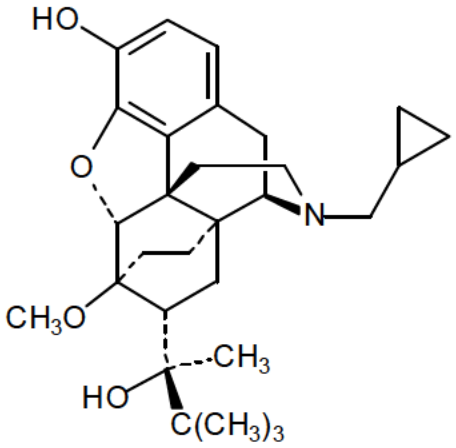
The Applicant has been advised by DEA that both the physician who prescribes Sublocade must be DATA-waived, or practicing in an OTP where DATA waivers are not required.

4 Product Quality

SUBLOCADE (buprenorphine extended release) injection is a clear, viscous, colorless to yellow to amber, viscous and sterile filtered buprenorphine non- aqueous solution for injection aseptically filled in syringes.

The active ingredient in SUBLOCADE is buprenorphine free base, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist.

The molecular weight of buprenorphine free base is 467.6, and its molecular formula is $C_{29}H_{41}NO_4$. Chemically, buprenorphine is (2S)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol. The structural formula is:



Buprenorphine is dissolved in the ATRIGEL® Delivery System at 18% by weight. The ATRIGEL® Delivery System, which is composed of a biodegradable 50:50 poly(DL-lactide-coglycolide) polymer (PLGH), (b) (4), and N-methyl-2-pyrrolidone (NMP), a biocompatible solvent, (b) (4) Buprenorphine is released from the depot by diffusion.

SUBLOCADE is provided in dosage strengths of 100 mg and 300 mg. Table 1 presents the delivered amounts of the raw materials and the approximate delivered volume for the two dosage strengths.

Table 1 Amounts of Raw Materials and Delivered Volume for the Dosage Strengths

Amounts of Raw Materials and Delivered Volume for the Dosage Strengths

Raw Materials in SUBLOCADE	100 mg Dosage	300 mg Dosage
Buprenorphine	100 mg	300 mg
Poly(DL-lactide-co-glycolide)	178 mg	533 mg
N-methyl-2-pyrrolidone	278 mg	833 mg
Approximate Delivered Volume	0.5 mL	1.5 mL

SUBLOCADE is a drug/device combination product as defined under 21 CFR 3.2(e)(1) and produced as a single entity, i.e., a pre-filled syringe, presented in a sterile pre-filled syringe assembly and a pre-packaged sterile needle for injection. The needle ((b) (4)) packaged with the syringe has previously been approved, 510k number (b) (4) .

Figure 1 SUBLOCADE pre-filled syringe

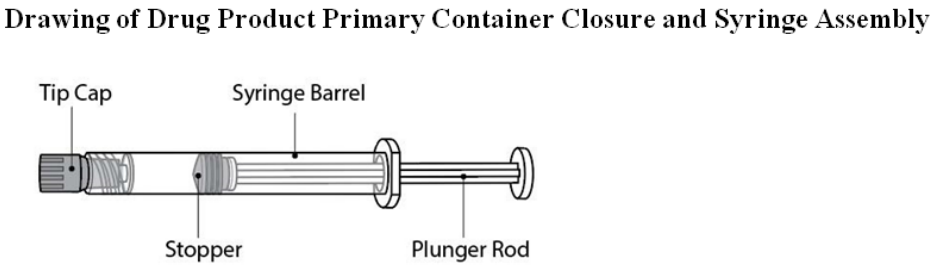
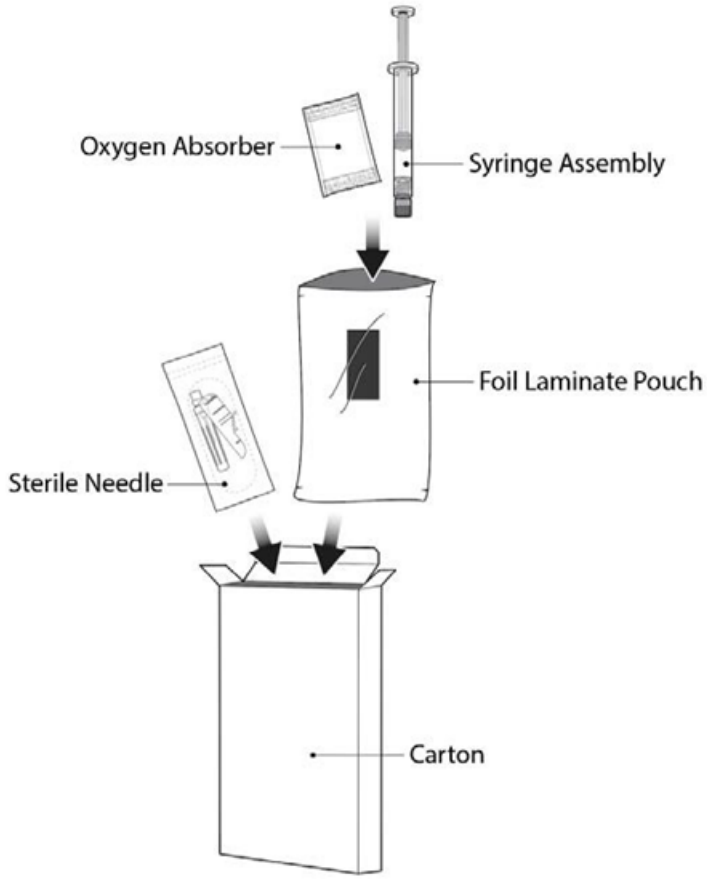


Figure 2 SUBLOCADE as provided



The active pharmaceutical ingredient attributes that have the potential to impact drug product quality are color, appearance of solution, related substances, (b) (4) content, bioburden and endotoxin. These attributes are controlled by the drug substance specifications.

The drug substance stability data adequately supports the proposed retest period (b) (4) The post-approval stability commitments are appropriate in confirming the initially assigned tentative retest period and will ensure the quality of the drug substance over the proposed retest period.

The characteristics (b) (4) [redacted]

(b) (4) [redacted] he sponsor has agreed to tighten the specification to

The quality of all excipients is adequately controlled with satisfactory specifications. The proposed excipient specifications ensure consistency of the process and quality of the final drug product.

The drug product specification is adequate to assure the identity, strength, quality, purity, and potency of the drug product so that future commercial production batches are comparable to the pivotal clinical batches for the clinical performance in terms of the safety and efficacy. The specification includes all of the critical drug product quality attributes. The batch analysis results are all within specification.

The regulatory analytical procedures are appropriate for the intended use, including method validation.

The drug product degradants are (b) (4) [redacted]. The proposed specifications are justified and/or qualified for safety based on nonclinical studies. Elemental Impurities testing will not be required for this drug product. No extraction studies produced any elemental impurities of toxicological concern. Six stability batches were tested for elemental impurities and none were found.
The sponsor proposes (b) (4) [redacted] s. The product stability studies and data support the proposed shelf life and storage conditions in the commercial container/closure system.

The firm adequately described all the processing steps involved in the manufacture of the proposed drug product. The flow diagrams included all the necessary critical process parameter operating ranges and in-process tests.

The drug product manufacturing process is designed (b) (4) . Procedures are in place to assure that the handling of the drug substance, excipients, components and drug product are performed to minimize microbial contamination, that all equipment is properly sterilized or sanitized and that the microbial quality of the environment is maintained

Facilities

The Office of Pharmaceutical Quality and Office of Compliance have determined all facilities to be acceptable, based on inspections performed during this review cycle (Indivior UK) or inspectional history (other sites) as noted below.

- Indivior UK Limited is the DMF holder and is responsible for manufacturing, packaging, release testing and stability testing of Steps (b) (4) for Buprenorphine. The inspection of the Indivior UK site was completed on 9/7/2017. No FDA-483 was issued. The inspector recommended approval for NDA 209819.

- (b) (4) is responsible for manufacturing Step (b) (4) for the (b) (4) The last inspection was completed on (b) (4) . The facility has a history of VAI and NAI inspections dating back to (b) (4) . This facility is acceptable for the intended operations stated in DMF (b) (4) and NDA 209819 based upon review of the firm's inspectional history.
- (b) (4) is responsible for drug substance residual (b) (4) testing and stability storage. The last inspection of the firm was completed (b) (4) and was the initial GMP inspection. No FDA-483 was issued. This facility is acceptable for the intended operations stated in NDA 209819 based upon review of the firm's inspectional history and confirmation of the capability to test for the presence of Heavy Metals.
- (b) (4) is responsible for microbiological testing of the drug substance. The last inspection was completed on (b) (4) . The 483 observations, the firm's response, and the EIR and associated exhibits from the (b) (4) inspection were reviewed and the firm's quality system is considered adequate and the inspection was classified as VAI. This facility is acceptable for the intended testing operations stated in NDA 209819 based upon review of the firm's inspectional history.
- (b) (4) is responsible for primary and intermediate packaging components; bulk formulation preparation, mixing and syringe filling. The last inspection was completed on (b) (4) . This facility is acceptable for the intended commercial operations stated in NDA 209819 based upon review of the firm's inspectional history.

(b) (4)

- This facility is acceptable for the intended operations stated in NDA 209819 based upon review of the firm's inspectional history.

(b) (4)

- This facility is acceptable for the intended operations stated in NDA 209819 based upon review of the firm's inspectional history.

In summary, drug substance, process, biopharmaceutics, microbiology, facilities, and drug product reviewers recommended approval of the application.

5 Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review was conducted by Gary Bond, Ph.D., and Elizabeth Bolan, Ph.D. The text below is largely excerpted from their review.

Potential systemic and local toxicity of the Sublocade drug product and the Atrigel Delivery System were evaluated in single-dose and chronic repeat-dose studies in rats and dogs and in reproductive toxicity studies in rats and rabbits. Potential genotoxicity was evaluated in vivo in rats. Generally, Sublocade and Atrigel (similar amount of NMP and PLGH as the respective Sublocade group) groups were tested. These studies lacked a saline control group, which complicates data interpretation; however, some separate studies were submitted that tested the Atrigel alone compared to a saline control arm.

Regarding local toxicity after subcutaneous dosing, the duration, frequency and severity of clinical signs and dermal observations at the injection site generally correlated with increasing volume of the Atrigel Delivery System administered. Expected effects of the injection were observed in the toxicity studies (and less frequently in the formulation development), which demonstrated swelling, abrasion, reddening and raised areas or masses, and dermal observations included edema, superficial/dermal irritation and erythema. Gross findings at injection sites in animals treated with Sublocade or the Atrigel Delivery System consisted of firm, dark or pale area/foci in the subcutaneous tissue, which correlated histologically in the single- and repeat-dose toxicology studies with subcutaneous granulomas, degenerate/necrotic cell debris, mononuclear cell infiltrate, fibroplasia and/or hemorrhage. Reversibility of local effects occurred after dosing ended over several months. The local effects are both the result of the vehicle and the buprenorphine.

No unanticipated systemic effects of acute dosing were observed. Notable single-dose effects in rats and dogs were related to buprenorphine (self-mutilation, pica, reduced food consumption and weight loss in rats and watery feces, no feces/constipation, emesis, decreased activity, changes in food consumption such as low or no consumption, and decreased body weight in dogs. After repeated dosing in rats (monthly for 6 months), evidence of increased stress was noted by the increased adrenal and decreased thymus weights.

There was an increased incidence of pancreatic acinar cell apoptosis (exocrine pancreas) in the studies testing Atrigel vehicle vs Sublocade. The Applicant attributed these to a stress response. The findings were not noted in published studies with NMP and were not expected to occur with PLGH. There are data to support the conclusion that decreased body weight gain, which can be a side effect of buprenorphine, can result in similar changes in the pancreas. However, based on these findings, the Applicant also included clinical monitoring for pancreatic function in their Phase 3 studies.

Early in development, the review team also commented on rat findings of alveolar macrophage infiltrates in lungs in both Atrigel vehicle and Sublocade groups that appeared dose responsive in incidence and reversible after discontinuation of dosing. This was intriguing given the intended route. However, additional rat studies that tested Atrigel vehicle vs saline either did not show the alveolar infiltrates in either group or demonstrated a comparable low incidence between the saline and Atrigel vehicle groups. Therefore, the findings are likely not toxicologically significant.

Reproduction toxicity studies conducted with Sublocade and Atrigel included fertility, embryo-fetal toxicity, and pre-/post-natal toxicity. These permitted updates to the relevant sections of the Subutex labeling to reflect accurate dose ratios for this product. Many of the adverse effects noted in these studies were present in both the Atrigel-alone arm and the Sublocade arms, with a few exceptions. These data suggest a potential risk of the vehicle in this formulation but also identified the potential for cranial malformations which appear to be due to buprenorphine alone. Review of the literature submitted by the Applicant suggests that there appears to be smaller safety margins for NMP than there are for buprenorphine. Further evaluation post-marketing is recommended.

In vivo micronucleus testing of Sublocade and Atrigel in a valid assay, yielded negative results, indicating that Sublocade and Atrigel are not genotoxic.

The carcinogenic potential of NMP has been described in the published literature. Studies in rats via the inhalation and dietary routes suggest no increased risk of carcinogenicity. However, a dietary study in the mouse demonstrated increased hepatocellular adenomas and carcinomas that appear to be treatment related. The clinical significance of rodent liver tumors is not clear. Many rodent hepatocarcinogens are not believed to have relevance to humans and there are signals in this study that suggest the same may be true to the NMP-induced mouse liver tumors. The review team suggests this be evaluated as a post-marketing study.

In regard to Product Quality (i.e., Drug Substance, Drug Product, Impurities, Excipients, and Extractables/Leachables), there were no nonclinical issues that preclude approval.

6 Clinical Pharmacology

The following summary of clinical pharmacology is taken primarily from the Division's proposed labeling, based on Clinical Pharmacology review by David Lee, PhD. Much of the general text about buprenorphine is identical to language in the Subutex label. Text specific to Sublocade is based on Indivior's development program.

Absorption

The pharmacokinetics (PK) of buprenorphine following subcutaneous injection of SUBLOCADE 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.

After SUBLOCADE injection, an initial buprenorphine peak was observed and the median T_{max} occurred at 24 hours after injection. After the initial buprenorphine peak, the plasma buprenorphine concentrations decreased slowly and steady-state plasma buprenorphine concentrations were reached by approximately Week 2. Observed mean buprenorphine concentrations levels for C_{avg}, C_{max} and C_{min} are presented in Table 2, from the Division's proposed labeling, based on Clinical Pharmacology review by David Lee, PhD. Numbers in bold italics highlight those parameters which substantially exceed those associated with the maximum recommended sublingual dose of Subutex, 24 mg/day.

Table 2 Comparison of buprenorphine mean pharmacokinetic parameters between Subutex and SUBLOCADE

Pharmacokinetic parameters	Subutex daily stabilization		SUBLOCADE		
Mean	12 mg (steady-state)	24 mg (steady-state)	300 mg# (1st injection)	100 mg* (steady-state)	300 mg* (Steady-state)
$C_{avg,ss}$ (ng/ml)	1.71	2.91	2.19	3.21	***6.54***
$C_{max,ss}$ (ng/ml)	5.35	8.27	5.37	4.88	***10.12***
$C_{min,ss}$ (ng/ml)	0.81	1.54	1.25	***2.48***	***5.01***

#Exposure after 1 injection of 300 mg Sublocade following 24 mg Subutex stabilization
*Steady-state exposure after 4 injections of 100 mg or 300 mg Sublocade, following 2 injections of 300 mg Sublocade

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 3. The PK parameters of steady-state exposure are based on 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 was full PK sampling with both 300mg and 100 mg after 4th injection.

Table 3 Pharmacokinetic Parameters of Phase 3 Dosing Regimens

Pharmacokinetic parameters	SUBLOCADE 300/100	SUBLOCADE 300/300
$C_{avg,ss}$ (ng/ml)	3.21 (25.5)	6.54 (31.7)
$C_{max,ss}$ (ng/ml)	4.88 (35.0)	10.12 (40.4)
$C_{min,ss}$ (ng/ml)	2.48 (30.0)	5.01 (31.9)

Source: Based on Table 13 in Clinical Pharmacology review.

Distribution

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

Elimination

Buprenorphine is metabolized and eliminated in urine and feces. The apparent terminal plasma half-life of buprenorphine following subcutaneous injection of SUBLOCADE ranged between 43 to 60 days as a result of the slow release of buprenorphine from the subcutaneous depot.

Metabolism

Buprenorphine is metabolized to its major metabolite, norbuprenorphine, primarily by CYP3A4. Norbuprenorphine can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity. Norbuprenorphine steady-state plasma concentrations in humans after subcutaneous injection of SUBLOCADE are low compared to buprenorphine (AUC norbuprenorphine/buprenorphine ratio of 0.20 to 0.40).

Excretion

A mass balance study of buprenorphine administered by IV infusion in humans 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 were 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).

Drug-Drug Interactions

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when SUBLOCADE is given concurrently with agents that affect CYP3A4 activity. The effects of co-administered CYP3A4 inducers or inhibitors have been established in studies using transmucosal buprenorphine. Drug interactions may differ based on the route of administration.

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.

The labeling will note the possibility of drug-drug interactions.

Specific Populations

Hepatic Impairment

As a post-marketing commitment associated with the approval of the Suboxone and Subutex applications, Indivior evaluated the effect of hepatic impairment on the PK of buprenorphine 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.

In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine were not clinically significant in comparison to healthy subjects without HCV infection.

The effects of hepatic impairment on buprenorphine PK after Sublocade injection have not been specifically studied. Because buprenorphine levels cannot be rapidly adjusted during Sublocade treatment, patients with pre-existing moderate to severe hepatic impairment are not candidates for treatment with SUBLOCADE, and patients who develop moderate-to-severe hepatic impairment while being treated with SUBLOCADE will need to be monitored for signs and symptoms of toxicity or overdose.

Removal of the Sublocade depot may be considered but is only feasible for the first 2 weeks after injection; moreover, residual plasma levels from prior injections would still be present.

Renal Impairment

Previous studies showed that less than 1% of buprenorphine is excreted unchanged in urine following IV administration. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine.

The effect of renal impairment on the pharmacokinetics of SUBLOCADE has not been studied. Clinical studies of SUBLOCADE did not include subjects with severe renal impairment.

Q-T evaluation

A particular issue of concern in this development program was the evaluation of buprenorphine's effects on cardiac conduction. Careful evaluation of the effects of buprenorphine on cardiac conduction was not performed during the development programs for Suboxone or Subutex. Based on *in vitro* binding studies, buprenorphine was not expected to have cardiac conduction effects.

However, a thorough QT (TQT) study was performed in a more-recent development program for a transdermal buprenorphine product used for analgesia. This study identified a signal for QT prolongation that was considered to meet the threshold for regulatory concern, but that was not of clear clinical significance. The dose studied was significantly lower than the labeled dose used for sublingual buprenorphine products for treating drug addiction, which is, in turn, lower than the Sublocade dose.

In view of the fact that Subutex and Suboxone had been marketed for several years before the signal was identified, letters requiring post-marketing studies of Q-T effects were issued to marketing application holders for buprenorphine products used for treatment of OUD. However, significant technical difficulties in designing these studies prevented them from being conducted according to the planned schedule. Therefore, Indivior was informed that data on the Q-T effects of Sublocade would be needed to support approval.

Rather than performing a specific QT study, Indivior provided data collected in their clinical trial program for Sublocade. The data submitted were deemed sufficient for filing by the interdisciplinary review team responsible for cardiac conduction study reviews (QT-IRT). The following assessment of the data is excerpted from the QT-IRT review by Dr. Gopichand Gottipati.

> The provided information in this application supports an absence of large mean (i.e., 20 ms) increases in the QTc interval for buprenorphine (RBP-6000) at the time of expected maximum buprenorphine exposure for RBP-6000 compared to a baseline where patients had been taking buprenorphine (with low systemic buprenorphine exposures).
>
> To assess the effects of RBP-6000 on the QT/QTc interval in NDA 209819, the sponsor conducted concentration-QTc analysis of pooled data from five clinical studies conducted in opioid-dependent patients.
>
> The ECG data collected in the pivotal efficacy study (RB-US-13-0001)… can support excluding large mean increases in the QTc interval, when comparing the QTc measurements at the maximum observed buprenorphine exposure compared to baseline. Please note that the baseline in the study was not a drug-free baseline, which should be taken into consideration when interpreting the results. This study included an open-label run-in of SUBOXONE sublingual film and a double-blind treatment phase with 2 dose levels (300/100 mg RBP-6000 and 300/300 mg RBP-6000) and placebo. At multiple visits, 12-lead ECGs were recorded as well and the sponsor was encouraged to include collection of 24-h holter recordings. The following observations support excluding large mean increases in the QTc interval:
>
> - No large increase in the mean (upper 95% CI) ΔQTcF at the time of mean maximum concentration (T_{max}) on Days 113 (T_{max} after 5th injection) or 141 (T_{max} after 6th injection) [300/100 mg: -2.5 ms (2.3 ms); 300/300 mg: 0.2 ms (6.7 ms)]. The exposures on Day 141 correspond to a ~5 and 10-fold increase for 300/100 mg and 300/300 mg respectively, in buprenorphine exposure compared to baseline. For patients on placebo, the maximum mean ΔQTcF was -5.9 ms (4.5 ms).
>
> - Few QTc categorical outliers in the Phase 3 study (RB-US-13-0001) and its open- label extension. A total of 10 (1.2%) patients had a change from baseline QTc ≥60 ms and 2 (0.2%) patients had QTcF >500 ms. These cases were confounded with non-negative urine drug tests. There were no QTc outliers in the placebo arm.
>
> - Absence of clinically significant ventricular tachyarrhythmias based on evaluation of 24-h holter recordings at each dosing visit.

Indivior performed concentration–QT analysis from ECG data collected from pooled studies in their development program, and concluded that there was no relationship between

buprenorphine concentration and QTc prolongation. However, the QT-IRT review team did not find the concentration-effect analysis appropriate because:

- The ECG acquisition and ECG measurement at baseline and during the treatment phase were different across studies.
- The study control procedures (e.g., placebo control, patient handling) were different across studies.
- There was a lack of a well-defined baseline, due to co-administration of SUBOXONE SL during induction/run-in, as well as an appropriately matched placebo group across studies.
- There was no study which included a positive control or had a substantial large exposure margin to waive the requirement for a positive control.

To explore the changes in QTc as it relates to exposure, the QT-IRT reviewer instead evaluated the data collected in the Phase 3 trial (RB-US-13-0001), as it was a blinded study with two dose groups and placebo. The C_{max} after the 6th injection (day 141) were ~5 and ~10-fold higher for the two dose groups respectively, compared to concentration at "baseline." At the visit with the maximum change from baseline, a mean ΔQTc and 95% upper CI of -5.9 ms (4.5 ms) was observed for placebo and -2.5 ms (2.3 ms) and 0.2 ms (6.7 ms) was observed for 300/100 and 300/300 mg respectively. There were no QTc values exceeding 480 ms and no ΔQTc values exceeding 60 ms at the C_{max} for the 5th and 6th injection. These data suggest an absence of a large difference in the QTc effect in the exposure range studied.

The review also included categorical analysis of the sponsor's submitted data, and assessment of cardiac safety. Based on analysis of outliers and categorical changes, a similar proportion of PR and QRS outliers between the two treatment groups and placebo in Study RB-US-13-0001, and few QTcF outliers were observed.

Regarding the adverse events in the clinical program, the reviewer noted:

> For the overall developmental programme, there were no cardiac events of syncope, seizures, ventricular arrhythmias, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths reported. 5(0.9%) of 504 subjects experienced TEAE's of QTc prolongation in Phase 3 Double Blind study (RB-US13-0001) of which 4 events were assessed as not related and 1 event was assessed as related to RBP-6000 with a possible confounding factors, considered completely recovered and clinically stable. Relative to the known Cardiac safety profile for buprenorphine, there were no unexpected safety findings and no new safety signals identified.

Indivior also conducted two nonclinical Good Laboratory Practices (GLP)-compliant toxicity and toxicokinetic studies in beagle dogs that also evaluated the cardiovascular safety of buprenorphine. According to the Sponsor, the results from these studies demonstrated a lack of hERG blockade although both studies had initial Day 1 QTc prolongation. The Sponsor noted that "the magnitude of these changes were mild and did not decrease with persistent dosing in either study. As there was no QTc prolongation on Day 14 (b) (4)) or at Week 4

(b) (4)),” the Sponsor’s expert report speculated that the QTc prolongation noted at Day 1 was unlikely to be related to hERG blockade. It was postulated that the QTc interval prolongation in these studies reflects acute test article-related effects on autonomic tone as reflected by associated neurological and gastrointestinal signs.

Overall, the data are reassuring in excluding large increases in QT interval, despite the high plasma exposures in the Sublocade studies.

7 Clinical Microbiology

N/A

8 Clinical/Statistical- Efficacy

The review of efficacy of RB-6000 focused on the findings from an inpatient opioid blockade study (RB-US-13-0002) and a randomized, double-blind, placebo-control efficacy study (RB-US-13-001)

8.1 Blockade study (RB-US-13-0002)

The primary review of the blockade study was performed by CSS Medical Officer, Dr. Alan Trachtenberg, and Biostatistics Reviewer, Wei Liu.

8.1.1 Design and Endpoints

Study RB-US-13-0002 was a double-blind, placebo-controlled, multiple-dose study in non-treatment seeking subjects with moderate to severe OUD to evaluate blockade of the intramuscular (IM) hydromorphone (HM) subjective effects by SC depot injections Sublocade. Buprenorphine plasma levels and the safety of SC injections were also examined.

Subjects were admitted to an inpatient unit, started and stabilized on Suboxone [buprenorphine/naloxone] sublingual film with doses of 8-24 mg/day. Stabilization was followed by randomized assignment of subjects to order of challenge presentation. One final baseline 3 day HM challenge set, while on SL BPN (days -4 to -1, referred to as “week 0”) was followed by the treatment period (for all sequence groups) of Sublocade injections, once per month for 2 months, starting on treatment day 1, followed with recurring weekly 3-day challenge sets (0 mg, 6 mg or 18 mg IM HM) in changing order.

The study consisted of a Screening Phase, a Qualification Phase (Baseline HM Challenge Phase), an Induction-Stabilization and Opioid Blockade Testing Phase, and a Treatment Phase (Figure 3). Eligible subjects were admitted to the clinical facility and established their final qualification by responding appropriately to IM HM and differentiating it from placebo (defined as having a “Drug Liking” VAS score of at least 40 mm [out of 100 mm on a unipolar scale anchored by “none” and “extremely”) following administration of 18 mg HM Qualified subjects entered into the Induction-Stabilization Phase of the study were they received 8 to 24 mg SL buprenorphine.

In addition to serving as the Qualification Phase of the study, VAS scores from this first 3-day

challenge set were recorded as pre-BUP baseline data, and referred to as "Week -1" in the data analysis. Following qualification, the subjects were then inducted and stabilized on Suboxone SL from Day -14 (Day -13 if the subject was not having withdrawal) through day -1.
On Day 1, subjects who still met all criteria discontinued SL BUP and received their first injection of RBP-6000 (initiating the treatment period (Figure 4)).

Subsequently, subjects were released from the clinical facility on Day 2.

Figure 3 Study RB-US-13-0002 Schematic

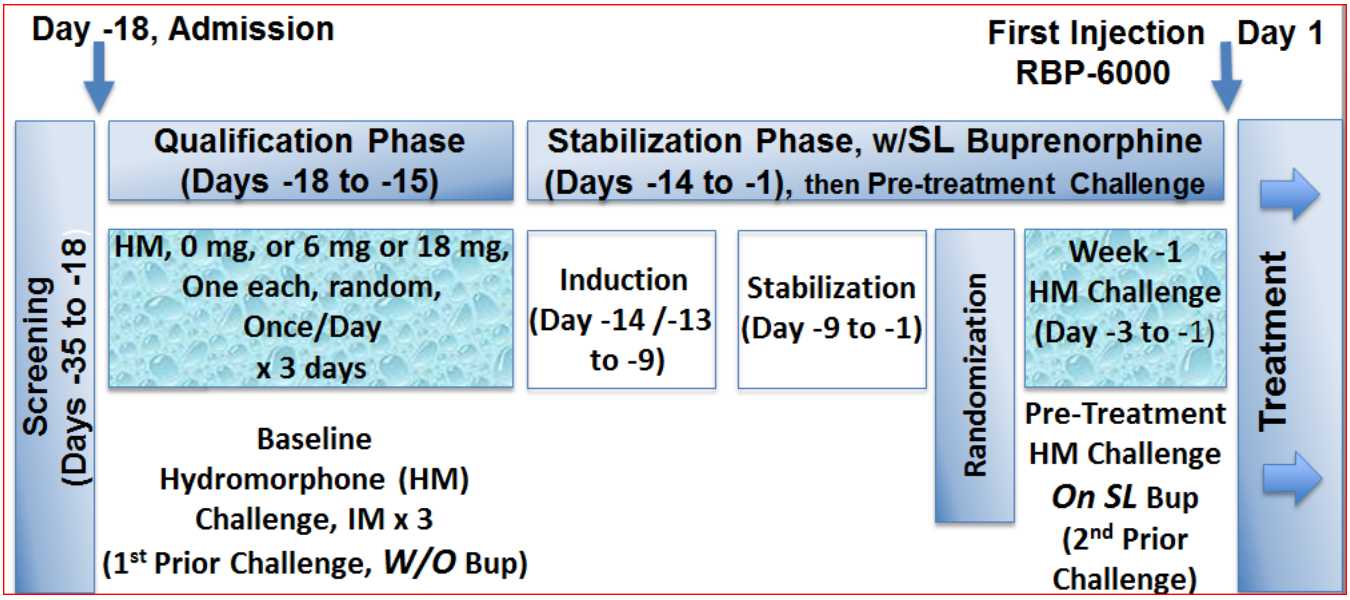
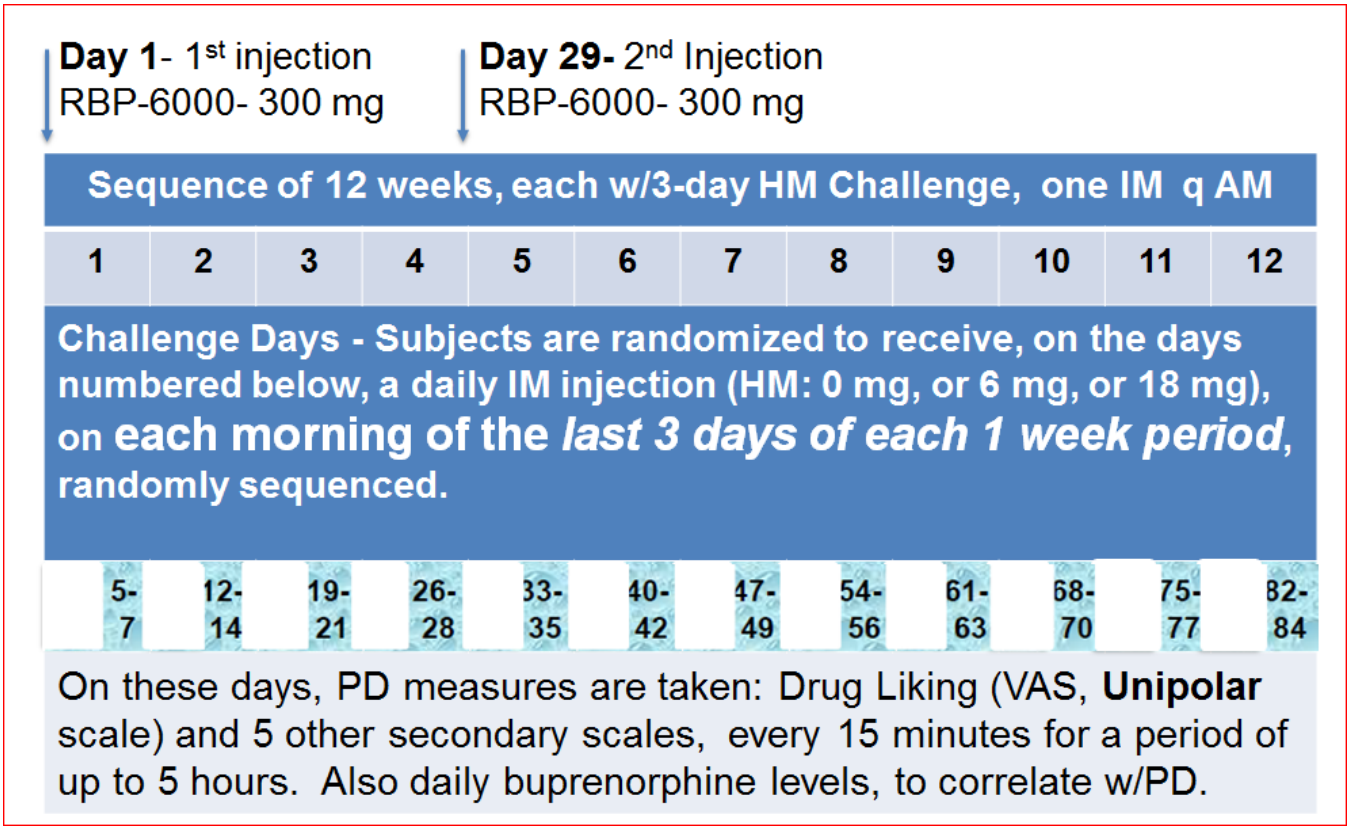


Figure 4 Study RB-US-13-0002 Treatment Phase



They returned to the clinical facility for the 3 consecutive days of HM challenge on Days 4, 11, 18, and 25. Following a second injection of Sublocade on Day 29, subjects were released from the facility on Day 30. Subjects returned to the facility for the 3 consecutive days of HM challenge on Days 32, 39, 46, 53, 60, 67, 74, and 81.

The study was primarily intended to demonstrate, following 300 mg SC of RBP-6000, that "Drug Liking" scores measured after challenge with 6 mg or 18 mg of IM HM (a C-II narcotic full μ-opioid agonist) were non-inferior to (not liked better than) those measured after challenge with an IM placebo injection. Under a full blockade of subjective opioid effects by BUP treatment, there should be no significant subjective differences between placebo injections and HM injections. Subject's response to an opioid challenge under blockade was measured each week for 4 weeks following injection #1 of RBP-6000 on Study Day 1 (Figure 1). Subjects were further followed for another 8 one-week intervals after a second 300mg dose of RBP-6000 on Study Day 29. "Drug Liking" was measured by subject report using a unipolar 100 mm visual analog scale (VAS), with the scale anchored by "none" and "extremely." This was obtained just prior to injection, then 15, 30, 45, 60 minutes and then every 15 minutes for up to 5 hours after IM injection. Other subjective drug effects were also measured concurrently by VAS including "Any Drug Effect," "Good Drug Effect," "Bad Drug Effect," Sedation," and "High." The reinforcing effects of each challenge day's randomized IM morning challenge were also evaluated in a choice task in which subjects were offered a series of 12 similar tasks delivering long series of repetitive clicks on a computer mouse, to "work" for "rewards" of either a repeated 1/12 fraction of that morning's total HM challenge dose, to be cumulated together for re-

administration in one dose that evening, or to choose cash.

The primary outcome, opioid blockade by RBP-6000, would be established by failure to discriminate blinded doses of 6 or 18 mg IM hydromorphone from placebo, through the first 4 weeks following the first injection of RBP-6000. The purpose of doubling the duration of evaluation after the second injection to 8 more weeks was to determine if opioid blockade was extended beyond the dosing interval of 4 weeks and to see if the subjective effects VAS scores, and ability to discriminate HM from placebo, returned to baseline over the 5-8 weeks post 2nd injection, as if a 3rd monthly injection had been missed.

8.1.2 Population

Thirty-nine subjects (of the 342 males and non-pregnant females with moderate to severe OUD who consented) qualified with a peak "Drug Liking" VAS score of at least 40 mm (out of 100 mm on a unipolar scale anchored by **"**none**"** and "extremely") after 18 mg HM IM and at least a 20 mm difference in "Drug Liking" between 18 mg HM and IM placebo were randomized into the different sequence groups. All 39 subjects were included in the safety analysis population. One of these did not complete and 38 subjects were included in the intent-to-treat (ITT) population. The 12 weeks of the treatment period were completed by 30 subjects (77%) and 9 subjects (23%) withdrew from the study. There were 3 subjects who withdrew because of physician decision or self-withdrawal (none due to AEs) and 3 subjects were lost to follow-up. Baseline demographics for the 39 subject Safety Population are shown in the table below (Dr. Trachtenberg's Table 2).

Table 4 Study RB-US-13-0002 Summary of Demographics (Safety Population)

	Category or Statistic	Overall N=39
Gender - n (%)	Male	35 (89.7)
	Female	4 (10.3)
Race - n (%)	White	25 (64.1)
	Black or African American	12 (30.8)
	Native Hawaiian or Other Pacific Islander	0 (0.0)
	Asian	2 (5.1)
	American Indian or Alaska Native	0 (0.0)
	Other	0 (0.0)
Ethnicity - n (%)	Hispanic or Latino	1 (2.6)
	Not Hispanic or Latino	38 (97.4)
Age (yr)	N	39
	Mean	34.6
	SD	8.93
	Median	34.0
	Min, Max	20, 55
Weight (kg)	N	39
	Mean	79.55
	SD	11.178
	Median	78.40
	Min, Max	60.9, 102.5
Height (cm)	N	39
	Mean	176.99
	SD	6.421
	Median	176.50
	Min, Max	165.5, 197.0
BMI (kg/m²)	N	39
	Mean	25.35
	SD	3.017
	Median	25.20
	Min, Max	20.7, 31.5
Nicotine Use (yr)	N	36
	Mean	19.03
	SD	8.962
	Median	20.00
	Min, Max	5.0, 44.0
N = number of subjects; n = number of subjects in a subset in a given category		

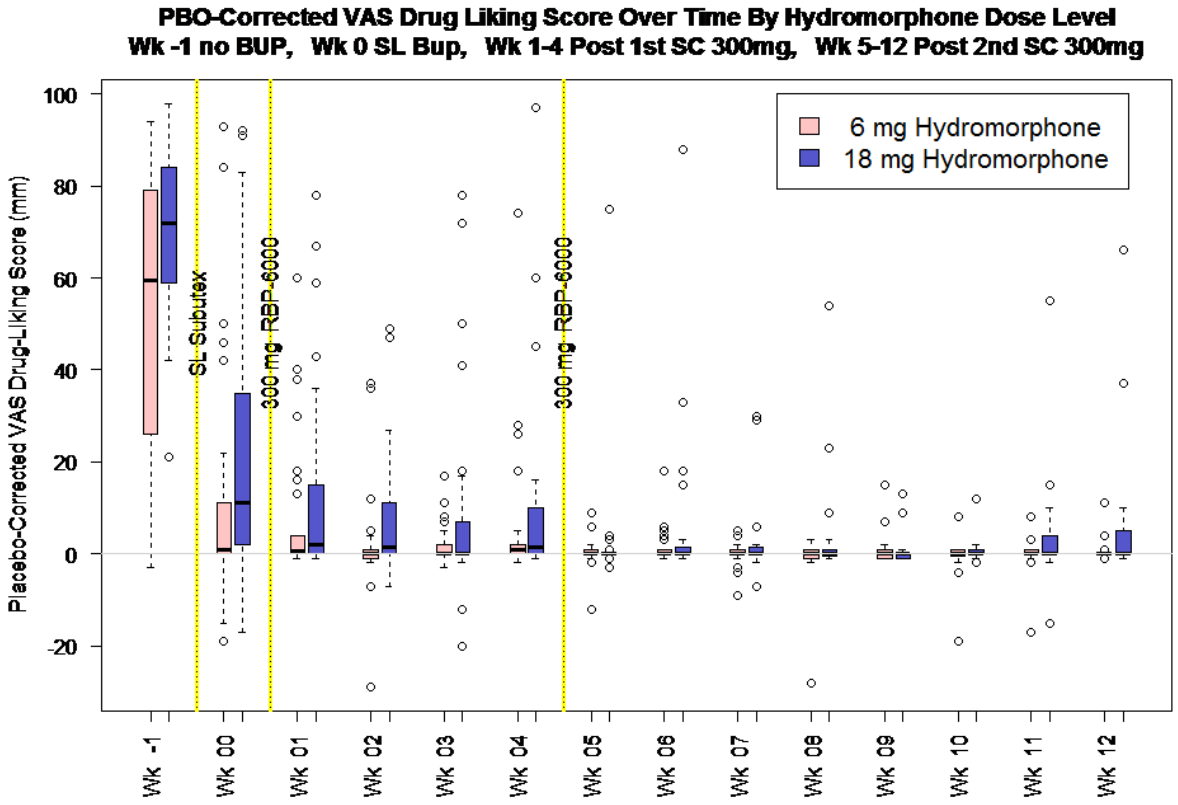
The Sponsor's analysis originally examined the "Drug Liking" effect, as measured from the VAS every 15 minutes, and took the mean of those from the entire 5-hour period following each day's challenge injections, and averaged those observations to arrive at an E_{mean}. This was then used for comparisons between the drug liking effects of placebo and HM. The recommended approach for human abuse liability studies is to compare the maximum effect, not the mean effect, because the maximum is considered more clinically-relevant, as noted in *2017 FDA Guidance for Industry Assessment of Abuse Potential of Drugs.*[4]

Additionally, the Sponsor's analysis applied a non-inferiority (NI) margin of 11 to the VAS measures from their Unipolar Scale of Drug Liking. The NI margin of 11, recommended in guidance, had been derived and standardized for data from Bipolar Scales. When re-analyzed by Dr. Liu using the Emax scores, the data did not support the conclusion that blockade was demonstrated. However, a more appropriate NI margin was determined, as detailed in Dr. Wei Liu's Statistical Review and Evaluation and this analysis supported the conclusion that Sublocade 300 mg, provides significant attenuation of the reinforcing subjective effects of 6 to 18 mg of IM HM, from the first week to the first month following the first SC injection. Dose accumulation after a second monthly 300 mg dose provides effective blockade of the reinforcing subjective effects of up to 18 mg of IM HM. Significant attenuation of opioid effect continues for more than 4 weeks, even after the end of a monthly dosing period, into the 2nd month if the monthly injection is missed.

The figure below, generated by Dr. Michael Bewernitz of the Office of Clinical Pharmacology, illustrates the maximum drug liking scores at each challenge. In the figure, vertical yellow lines indicate the time that SL buprenorphine was initiated as well as the time of SC injections of 300 mg Sublocade. The red and blue boxplots represent the placebo-corrected Emax drug-liking score distribution observed during the hydromorphone challenge for 6 and 18 mg, respectively, with circles representing outliers. (Each individual's maximum liking score for placebo for that set of challenges was subtracted from the individual's maximum liking score for the hydromorphone challenges.) The 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.

[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

Figure 5 Distribution of Placebo-Corrected Drug-Liking Scores by Hydromorphone Dose Level and By Week



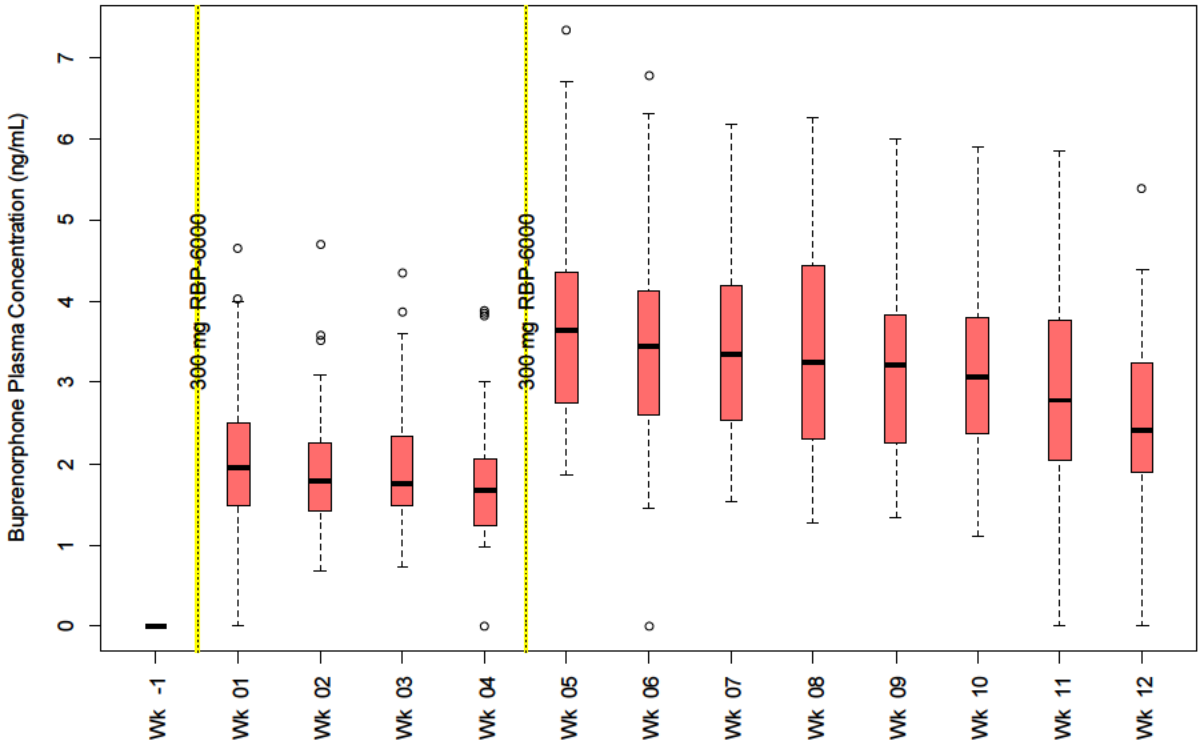
Note: "Week -1" is actually almost 2 weeks separated from Week 0. However, Week 1 – Week 12 are actually spaced 1 week apart.

Positive values mean hydromorphone is liked more than placebo; a zero value means hydromorphone is liked the same amount as placebo; negative values mean hydrophone is liked less than placebo. The decrease in a positive placebo-corrected drug-liking value after Sublocade initiation compared to before Sublocade initiation is consistent with Sublocade 'blocking" some of the subject's positive response for hydromorphone. A decrease in placebo-corrected drug-liking to a value near zero is consistent with a near complete blockade of drug-liking.

This figure illustrates that drug liking was, as expected, highest during the baseline or qualification period, Week -1, where the hydromorphone challenge was conducted in the absence of buprenorphine. Drug-liking was reduced after stabilization on SL buprenorphine at 8 mg once daily to 24 mg once daily (Week 0) compared to baseline or qualification period (Week -1). Drug-liking was further reduced after RBP-6000 administration (at and after Week 1) compared to drug-liking assessed during SL buprenorphine (Week 0) as well as baseline or qualification phase (Week -1). More effective blockade of "drug liking" for the 6 mg hydromorphone dose level than for 18 mg was noted. Additionally, blockade was more effective after the second Sublocade administration (at and after Week 5), likely due to greater buprenorphine concentrations achieved during this period. However, the figure also illustrates the substantial inter-individual variability in response, with outliers at each time point who did not, apparently, experience a blockade of hydromorphone effects. Fewer outliers are seen over time.

Dr. Bewernitz also analyzed the dose-response relationships in this study. PK and PD data were available from 38 subjects. PK data were buprenorphine plasma concentrations measured immediately before the hydromorphone challenge. Initial analysis indicated that hydromorphone administration did not affect buprenorphine exposure, and therefore the data were pooled to include all buprenorphine exposures during all 3 hydromorphone test sessions per week. The figure below 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).

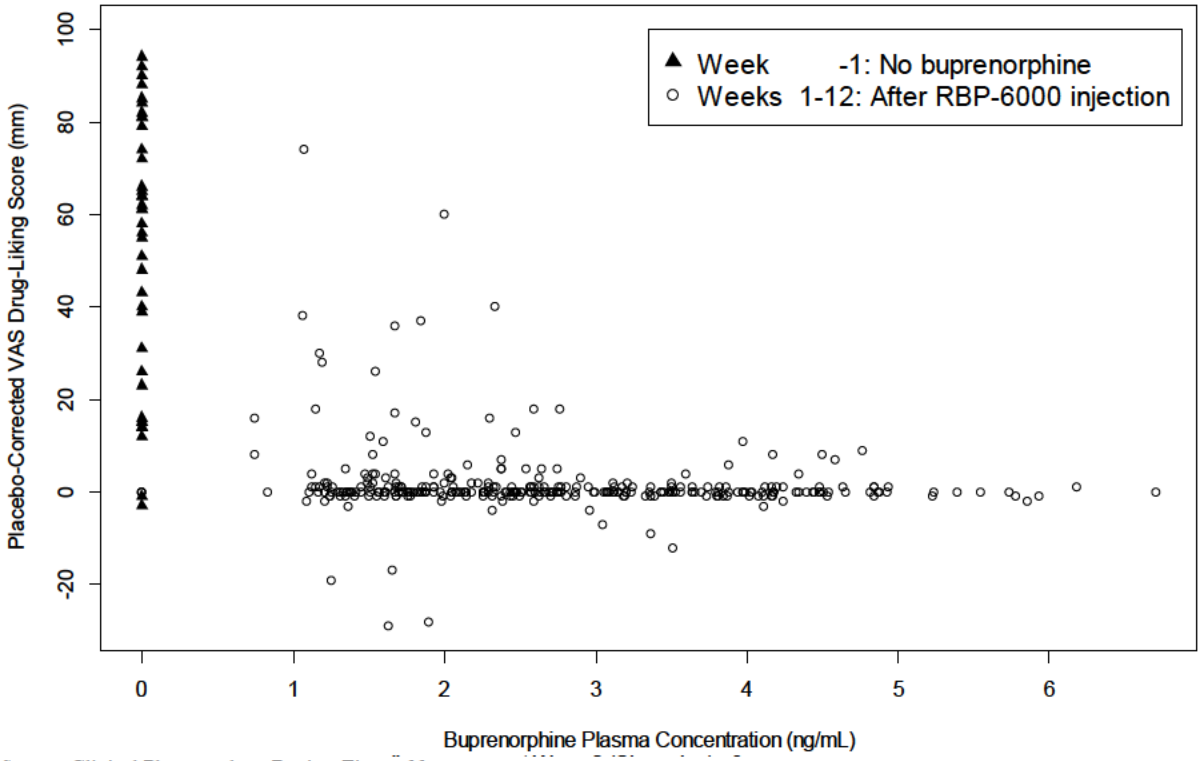
Figure 6 Distribution of Buprenorphine Concentration Measured Immediately Prior to Hydromorphone Session By Week



*Vertical yellow lines indicate the timing of SC injections of RBP-6000.
Source: Clinical Pharmacology Review Figure 63

The pharmacodynamic (PD) measurement was the maximum drug-liking assessment (E_{max}) during each 3-day hydromorphone test session. 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).

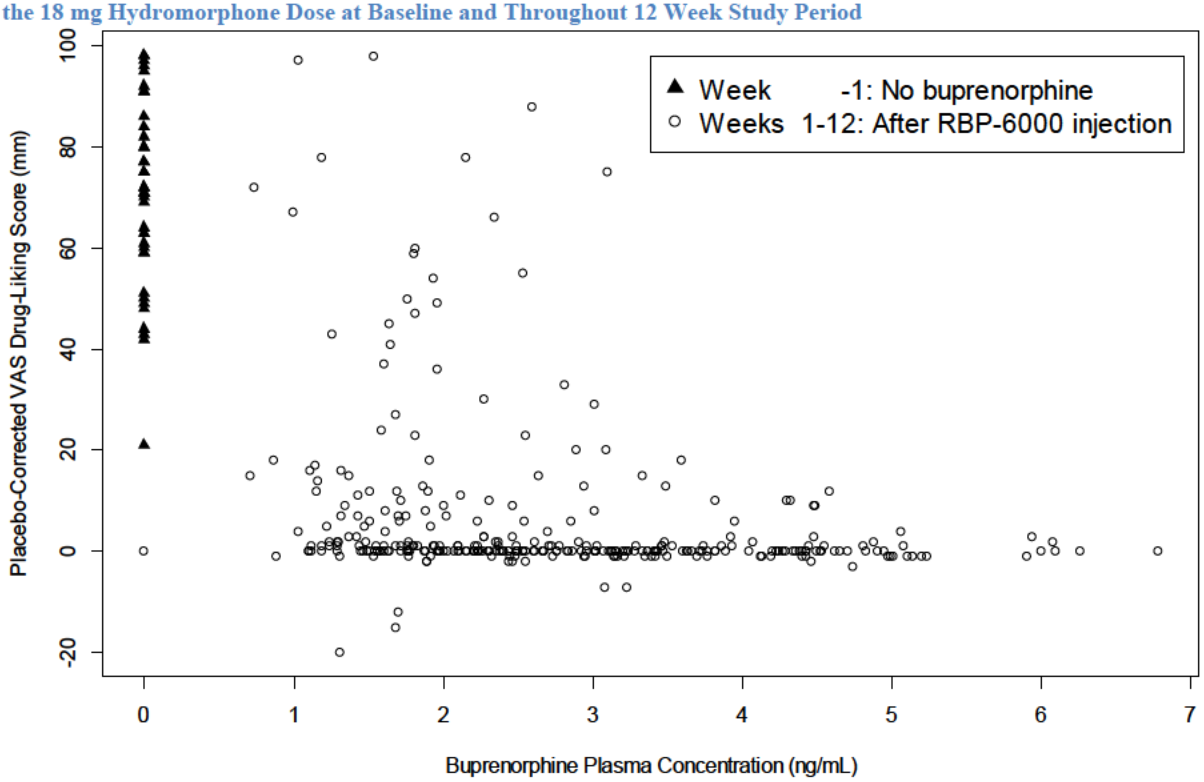
Figure 7: Scatter Plot of Placebo Corrected Drug-Liking Scores With Corresponding Buprenorphine Concentration for the 6 mg Hydromorphone Dose at Baseline and Throughout 12 Week Study Period



Source: Clinical Pharmacology Review Figure 66

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.

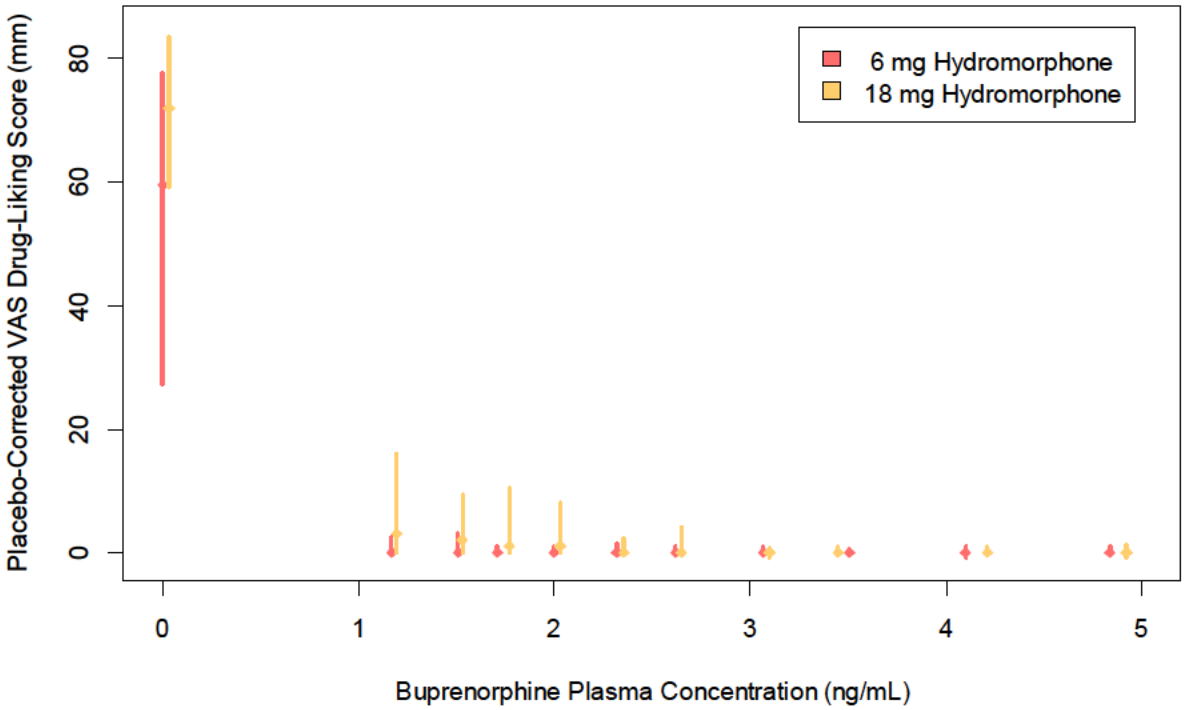
Figure 8 Scatter Plot of Placebo-Corrected Drug-Liking Scores With Corresponding Buprenorphine Concentration for the 18 mg Hydromorphone Dose at Baseline and Throughout 12 Week Study Period



Source: Clinical Pharmacology Review Figure 67

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 9 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



Source: Clinical Pharmacology Review Figure 68

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.

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, 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, approximately one-half of the subjects appeared to present abrupt changes in the drug-liking scores from week to week. that do not appear to correlate with the PK profile. These observations suggest that, in addition to buprenorphine concentration, other factors which are currently unknown, are likely influencing the drug liking scores.

8.2 Efficacy Study (RB-US-13-0001)

8.2.1 Study Design and Endpoints

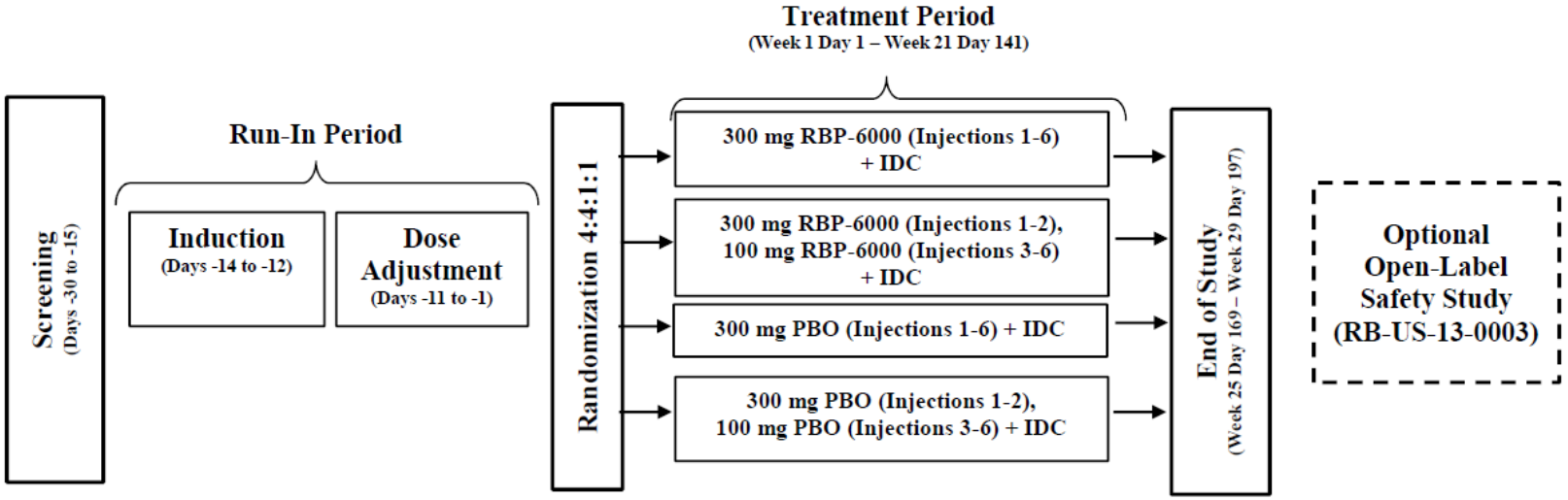
Study RB-US-13-0001 was a randomized, double-blind, placebo-controlled, parallel group, multicenter study to assess the efficacy, safety and tolerability of multiple SC injections of RBP-6000 (100 mg and 300 mg) over 24 weeks in treatment-seeking subjects with opioid use disorder. The study consisted of a screening phase up to 2 weeks, an open-label run-in phase up to 2 weeks, a randomized, double-blind treatment phase of 24 weeks, and a follow-up period. The study randomized subjects from 33 sites in the United States. Subjects who completed this study were eligible to enter a long-term safety extension study (Study RB-US-13-0003).
All subjects who entered the open-label run-in induction phase were treated with SUBOXONE (buprenorphine/naloxone) sublingual film for 3 days followed by a dose-adjustment period of 4 to 11 days. Subjects who completed the open-label run-in phase and met randomization criteria were randomized on Day 1 of the double-blind treatment phase. Study drug was administered as a SC injection every 4 weeks for a total of 6 doses. Subjects also received manual-guided behavior counseling/individual drug counselling (IDC) at least once per week throughout the study. To be eligible for randomization, subjects should have had no significant opioid craving (≤ 20 mm on the Opioid Craving Visual Analog Scale) or withdrawal (a score of ≤ 12 on the Clinical Opiate Withdrawal Scale) after at least 7 days of SUBOXONE sublingual film therapy. Eligible subjects were randomized in a 4:4:1:1 ratio to receive the one of the following regimens:

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

A schematic diagram is shown below. Time-and-events tables are found in the Appendix.

Figure 10 Pivotal safety and efficacy study (13-0001) scheme

Figure 1 Study Design



IDC=individual drug counselling

Note: Subjects received IDC during the double-blind treatment period. A total of 163 of the 504 subjects enrolled (32.3%) received a 5-day SUBOXONE taper as follows: Day 1 (6 mg), Day 2 (4 mg), Day 3 (4 mg), Day 4 (2 mg) and Day 5 (2 mg), according to Amendment 2.

Sources: RB-US-13-0001 CSR Figure 1

After the study had started, the protocol was amended to include a 5-day SUBOXONE sublingual film taper. The purpose of taper was to mitigate the potential for withdrawal signs and symptoms in placebo-treated subjects, which could contribute to early drop-out, and to facilitate preservation of the blind of the study. A total of 163 randomized subjects received a 5-day SUBOXONE sublingual film taper following the first injection of study treatment. After injection of study treatment, subjects were not permitted supplemental SUBOXONE sublingual film except for the 5-day taper that began on Day 1. Subjects who required additional supplemental SUBOXONE sublingual film or other sublingual buprenorphine pharmacotherapy after Day 1 were to be withdrawn for lack of efficacy and referred for appropriate treatment.
Following randomization, subjects were to return to the clinic weekly for urine drug screen (UDS), Timeline Follow Back (TLFB) interviews, assessments using Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), and Opioid Craving Visual Analog Scale (VAS). The TLFB interview asked subjects to retrospectively estimate their drug use in the 30 days prior to screen at the screening visit and since the last visit at all subsequent visits.

The primary efficacy endpoint was the cumulative distribution function (CDF) of the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use[5] collected from Week 5 through Week 24. The purpose of analyzing efficacy starting from Week 5 instead of Week 1 was to allow subjects to stabilize in treatment. The percentage of negative drug use assessments was computed for each subject as the number of weeks of non-use divided by 20. For example, if a subject had 10 weeks of negative urine samples and TLFB self-report negative for opioids, the percentage negative assessments of this subject was 50%. The key secondary endpoint was treatment success, defined as any subject with at least 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Week 5 through Week 24. As described in Section 3.1.1, this was a pragmatic definition.

8.2.2 Demographics and Disposition

A total of 504 subjects were randomized, 100 to placebo, 203 to RBP-6000 100 mg group, and 201 to RBP-6000 300 mg group. The demographic and baseline characteristics were comparable across treatment groups (Table 5). The majority of the subjects were male (66%) and white (71%). Overall, about 44% of the subjects had history of injectable opioid use.

[5] Called "percentage abstinence" in the protocol. This term is misleading because patients might continue to use opioids without detection due to the urine toxicology collection schedule.

Table 5: Summary of Demographics and Baseline Characteristics

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

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

Approximately 60% of the subjects in RBP-6000 groups completed the study compared with approximately 34% in the placebo group. The dispositions of the two active treatment groups were similar. The most common reasons for discontinuation in both active treatment groups were "lost to follow-up" and "subject withdrew consent". The percentage of subjects that discontinued due to "lack of efficacy" or "subject withdrew consent" was higher in the placebo group than the active groups. Similar percentages of subjects in the three treatment groups discontinued due to "lost to follow-up".

Table 6: Subject Disposition

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

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

8.2.3 Statistical Methodologies

The primary efficacy endpoint was analyzed using the Wilcoxon rank-sum test. Efficacy analyses were conducted for the full analysis population (FAS), defined as all randomized patients who received study treatment. The Applicant excluded subjects from site 20 due to compliance issues. A sensitivity analysis including the subjects from site 20 produced similar results and the same conclusion. The two randomized placebo groups were combined and analyzed as one placebo group. Missing UDS samples and self-reports were imputed as positive in the primary analysis. The two RBP-6000 dose regimens were each tested against placebo at the 0.025 level.

8.2.4 Results and Conclusions

The Figure 11 below illustrates the CDF of percent negative urine samples for Weeks 5–24 with self-reported use incorporated as positive. The figures differ from the plot of a CDF which displays the percent of patients who had a given outcome or less. For this reason, a graph of a cumulative distribution function customarily rises from zero at the left to 100% at the right. In our presentations, the graphs show the percentage of patients who provided a given percentage of negative samples or better. The curves therefore fall from 100% at the left to 0% at the right. For example, in this study, approximately 35% of the patients in the active treatment groups had at least 70% of samples negative. The difference from placebo in the distribution function was statistically significant with p-value<0.0001 for each dose of the active treatment based on the Wilcoxon rank-sum test.

Figure 11: Cumulative Distribution Function of Percentage Abstinence

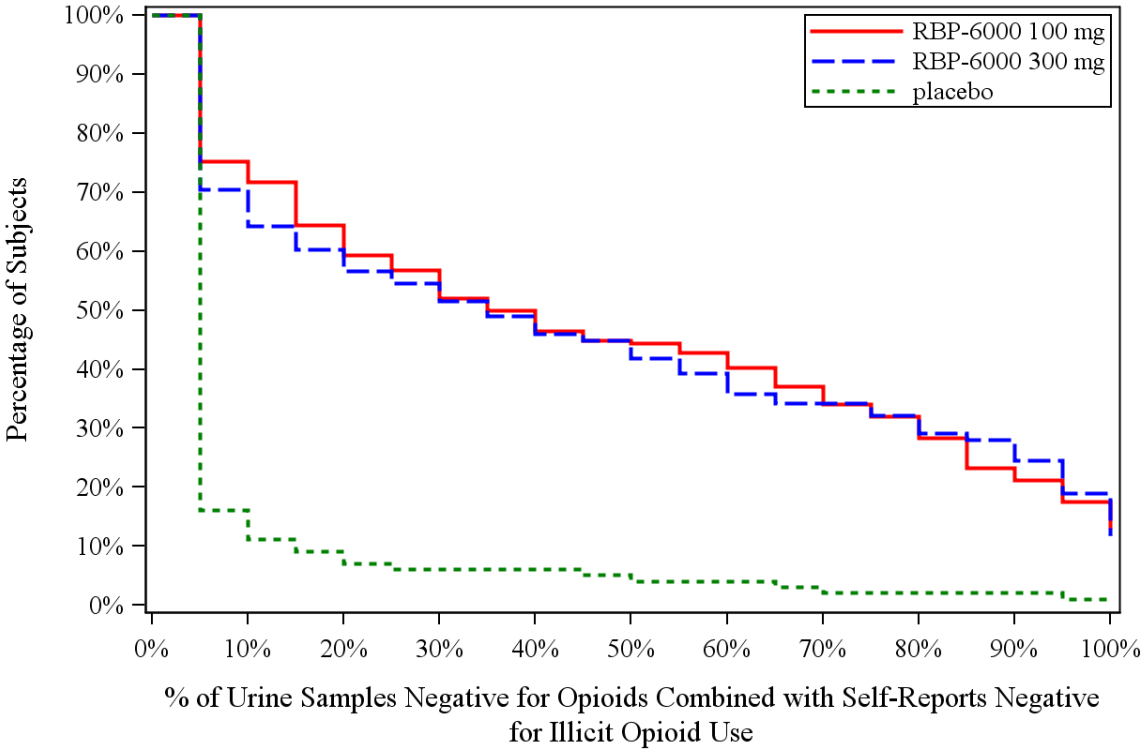


Table 7presents the CDF values of F**igure 11** at different percentage abstinence in 10% increments. As can be seen in F**igure 11** and

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Table 7, 12-13% of patients in each active treatment group had no positive or missing samples or self-report of illicit use over the 20-week efficacy ascertainment period. The pre-specified responder definition allowed four missing or positive samples out of the 20 collected. The proportion of patients meeting that criterion as well as the proportion who had no indicators of illicit use were both higher in each of the active treatment groups than the placebo group with nominal statistical significance based on Fisher's Exact test.

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Table 7: Cumulative Percentage Abstinence from Weeks 5 to 24

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

The overall percent of negative tests does not differentiate between, for example, a patient who is abstinent for half the study and then relapses to daily illicit drug use, a patient who continues to use illicit drugs daily for half the study and then stops completely, and a patient who uses intermittently, half of the days throughout the study. All of these patients might have 50% of their tests negative. To allow an appreciation of the temporal sequence of patients' test results, the graphic depictions below show the results of each urine test for each patient. They also distinguish between tests that were imputed as positive in the analyses because they were intermittent missing, or because a patient self-reported drug use, and actual positive tests.

In these subject-level presentations, each individual subject is represented along the y-axis. On the x-axis are the time points during which urine samples were collected. (In this study, urine samples were collected weekly). Blue circular dots are used to represent submission of opioid- negative urine samples at any time point, while red triangular dots are used to represent opioid-positive urine submissions. Ideally, a patient achieving treatment success would have many more blue data points than red data points, particularly along the right-hand side of the x-axis which represents longer periods of time on treatment. The data points that appear black in these presentations are '+' symbols and denote intermittent missing urine data. The red "x" dots indicate where urine samples were negative or missing but subjects self-reported opioids use.
Patients who did not complete the full study are shown at the top of each display and are sorted based on time in the study. Samples after the last dot in the row were missing and were imputed as positive for the purposes of analysis. Completers are shown in the bottom of each display, arranged by time to last positive sample.

Figure 12: Urine Opioid Screen Results for Individual Subjects

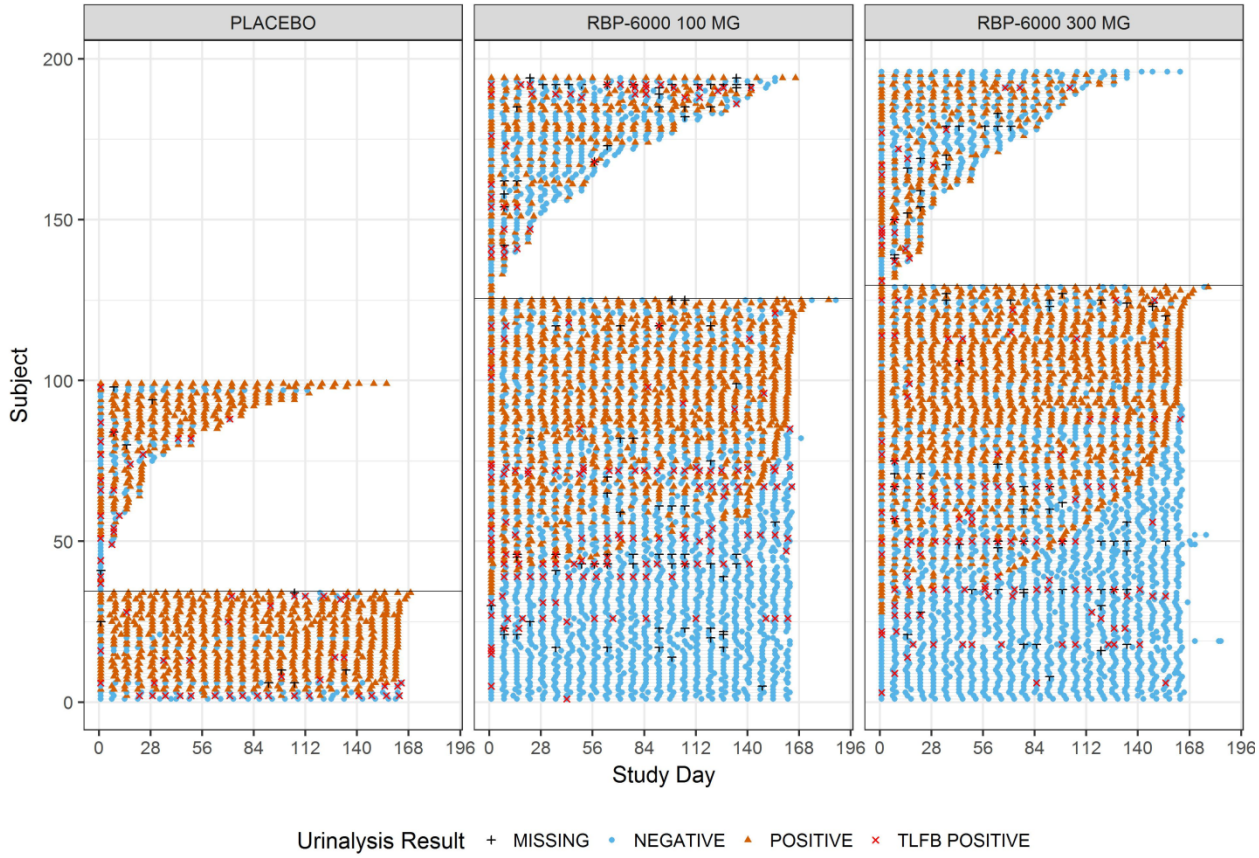


Table 8, below, illustrates the degree of concordance between urine test findings and self-report. This tabulation shows that the self-report of drug use was negative on over half the occasions on which the patient submitted a sample which was positive. Self-report contributed to detecting drug use in the presence of a negative urine sample in only about 5% of occasions.

Table 8: Urine results vs TLFB Week 5 to Week 24 (Excluding site 20)

	TLFB			
Urine test	Missing	Negative	Positive	Total
Missing*	3216 (33%)	41 (0.4%)	**18 (0.2%)**	3275 (33%)
Negative	37 (0.4%)	3377 (35%)	**223 (2%)**	3637 (37%)
Positive	30 (0.3%)	1841 (19%)	997 (10%)	2868 (29%)
Total	3283 (34%)	5259 (54%)	1238 (13%)	9780 (100%)

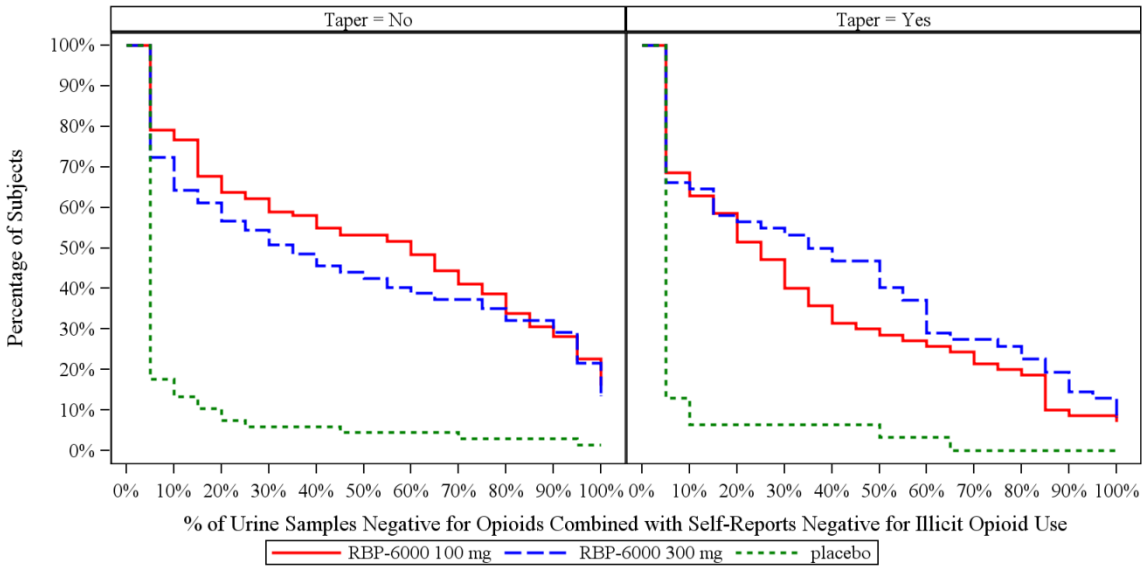
Source: Statistics Reviewer: Missing includes those due to dropouts.

To explore the impact of missing data due to subject discontinuation on the primary analysis, Dr. Li conducted several sensitivity analyses. Regardless of the assumptions for missing data due to subject discontinuations, all analyses supported the conclusion from the primary analysis.

Dr. Li also found that subgroup analyses based on sex, age, and race were consistent with the overall population.

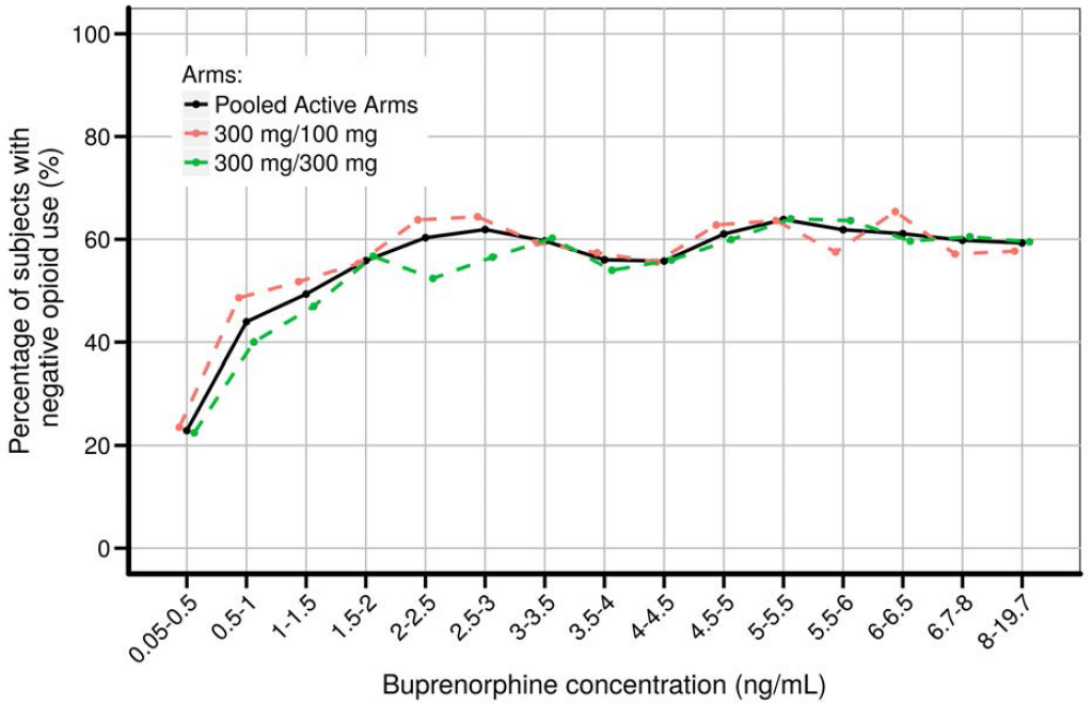
After the study was initiated, the protocol was amended to incorporate a taper at the end of the sublingual film run-in to mitigate the potential effects of abrupt discontinuation on patients blindly switched to placebo injections, which could increase the rate of discontinuations in the placebo arm and lead to a spurious conclusion about efficacy in that arm. A total of 163 (32%) subjects received a 5-day SUBOXONE sublingual film taper following the first injection of study treatment. The cumulative distribution functions of percentage abstinence are depicted by tapering status in
Figure **13**. The figures illustrate that there was no obvious difference in retention in the placebo group based on presence or absence of tapering.

Figure 13: CDF of the Percentage Abstinence for Subjects by Tapering Status



Indivior plotted the relationship between plasma exposures and drug use using data from this study. As shown in Figure 14, there is an apparent increase in response with increasing exposure up to approximately 2 ng/mL. There is an apparent "plateau" of where these responses are at their maximum at a range above 2-3 ng/mL.

Figure 14 Relationship Between the Proportion of Subjects with Negative Opioid Use and Buprenorphine Plasma Concentration (Study 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

Indivior performed exposure-response analysis for negative opioid using an E_{max} model. The results indicated that subjects who used illicit opioids via the injectable route had a 3.6 times greater EC50 (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 may require greater buprenorphine exposure to avoid illicit opioid use than patients who use illicit opioids by other routes.

Dr. Li performed a subgroup analysis by injection drug use status, incorporating the UDS results. It appears that injection drug users numerically responded to the high dose regimen RBP-6000 300/300 mg better than RBP-6000 300/100 mg based on the CDF curve plot below (Figure 15 and

Figure 16), however, the difference was not statistically significant.

Figure 15 CDF of percentage abstinence for injection drug users

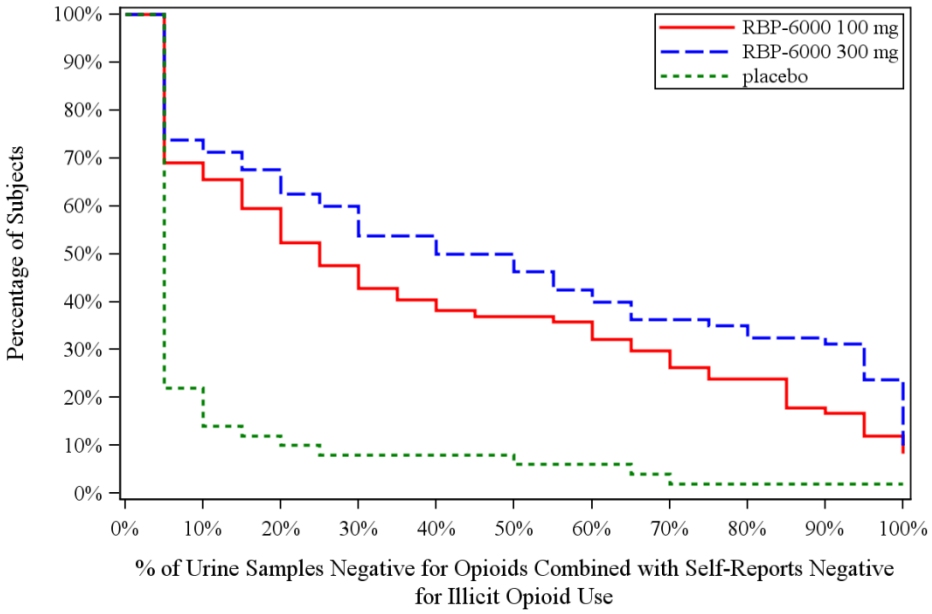
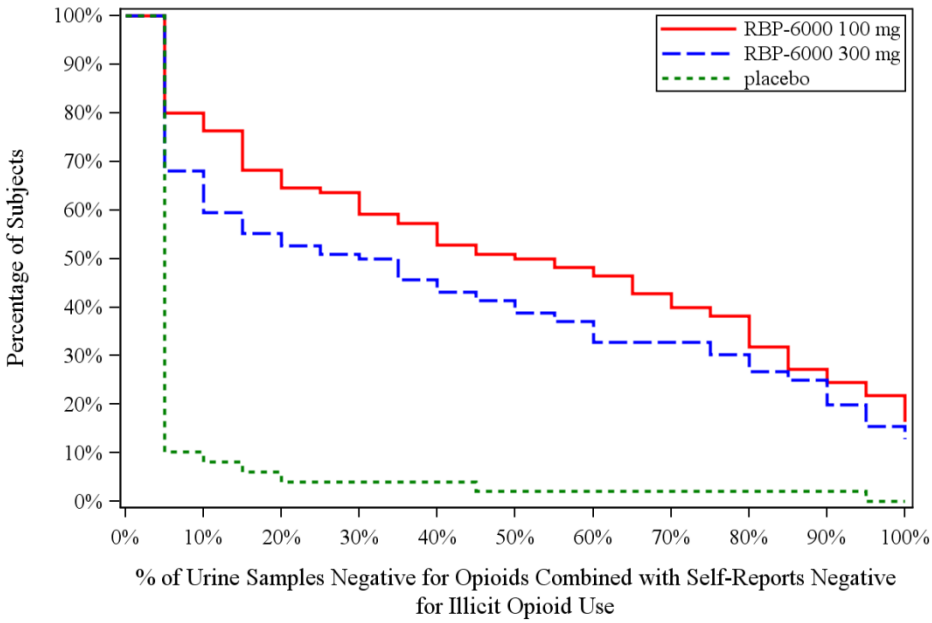


Figure 16 CDF of percentage abstinence for non-injection drug users



Additional explorations by Dr. Li also did not change the conclusions. These included inclusion/exclusion of Site 20, which had been excluded by the Applicant due to issues during the conduct of the trial; exclusion of a site (28) that was found during inspection to have a potential conflict of interest; analyses incorporating extra/unscheduled urine tests. The results were consistent with the primary analysis.

Analyses of secondary endpoints including COWS, SOWS and opioid craving VAS were also supportive of efficacy. However, these endpoints were not formally tested with prespecified multiplicity adjustment and Dr. Li recommended they not be included in labeling.

8.3 Discussion

The evidence of efficacy provided includes a single placebo-controlled efficacy study taken together with pharmacodynamic data showing that Sublocade blocks the effects of exogenously administered opioids for the entire inter-dose period.

In Study 13-001, there were weekly, scheduled, samples collected over 24 weeks. A CDF of patient responses was the primary endpoint, and the secondary endpoint was a responder analysis. The responder definition agreed to was 80% negative over Weeks 5-24, based on pragmatic considerations. Therefore, a responder is defined as a patient who provides self-report and laboratory evidence of absence of illicit opioid use on 16 of 20 scheduled weekly visits. Such patients may have a number of undetected occasions drug use; however the ability to attend study visits and provide negative urine samples over a 24-week period is nevertheless an indicator of some degree of clinical stability.

Notably, even using a responder definition of 100% of urine samples and self-reports present and negative, both regimens of Sublocade were shown to be superior to placebo. Contrary to many assumptions, the retention rate in the placebo group, while low, was not zero. Over one-third of the placebo-treated subjects completed the full 24 weeks of the study. However, the response rate even in completers was very low.

It should also be noted that the study employed an enrichment design. Only patients who could tolerate buprenorphine, reach a stable buprenorphine dose within about 2 weeks, and comply with returning to the study site through the run-in period could be enrolled. One-quarter of the patients who entered the run-in period were ultimately not randomized. This may explain, to some extent, the fairly good completion rate in the placebo arm. Although this enriched population may give a more optimistic picture of the product's efficacy than can be expected in a general population, the superiority to placebo is not expected to be affected.

No clear incremental benefit of the 300 mg/300 mg dose regimen was apparent. There is some suggestion that there may be subgroups of patients (e.g., those who use opioids by the i.v. route) who may benefit from the higher dose. Additionally, the PK/PD analyses of the blockade study reveal quite a bit of variability across subjects and the dose-response analysis suggests that higher doses may be needed for some subjects to experience full blockade.

The graphic displays of patient response allow us to appreciate that there were obvious differences in the patterns of drug use between active and placebo treatment arms, even among responders. It also makes clear that even some fully-compliant patients being treated with doses of buprenorphine that yield very high steady-state blood levels—expected to block the reinforcing effects of opioids—will continue to use illicit opioids despite treatment.

Nonetheless, Sublocade at the recommended regimen clearly provides blockade of effects of exogenously-administered opioids, and is superior to placebo in helping patients refrain from illicit drug use.

Taken together with previous evidence of efficacy for Indivior's Subutex product, these data provide the substantial evidence of effectiveness required by law [21 CFR 314.126(a)(b)] to support approval.

9 Safety

Safety data derive from Phase 1 PK studies, the Phase 3 blockade study and efficacy study described above, and a Phase 3 open-label study which included "rollover" patients from Study 13-001 as well as "de novo" patients. All patients, including those continuing from Study 13-001, began the open-label study with an initial run-in on transmucosal buprenorphine and two monthly doses of 300 mg, after which the dose could be adjusted by the clinician. This is referred to in tables below as "flex" dosing.

A total of 1083 subjects, ages 18-65 years, with opioid use disorder or opioid dependence received at least 1 SC injection of RBP-6000 across 7 studies over the clinical development program. A total of 235 subjects in Phase 1 and 2 studies received RBP-6000 a single dose or multiple doses ranging from 20 to 300 mg with 196 subjects at the 100 mg, 200 mg or 300 mg dose.

The extent of exposure in Phase 3 is shown in Table 9 and Table 10. In Phase 3, 313 patients received at least one dose (4 weeks) of the 100 mg dose and 848 received at least one dose of the 300 mg. These included 320 patients who were treated with the 300 mg/flex regimen for 48 weeks or longer, and 187 treated with 300 mg continuously for 48 weeks or longer.

Table 9 Phase 3 Safety Database

Study 13-0001 (NCT02357901) Up to 6 Injections			**Study 13-0003 (NCT02510014)**				**Total Subjects Exposed To** SUBLOCADE
			Roll-Over Up to 6 Injections			**De Novo Up to 12 Injections**	
300/100 Mg	**300/300 Mg**	PLA	**From 300/100 Mg To 300/Flex†**	**From 300/300 Mg To 300/Flex†**	**From Placebo To 300/Flex†**	**300/Flex**	
203	201	100*	112‡	113‡	32	412	848

*Not included in total subjects exposed to SUBLOCADE
† FLEX = 300 mg initial dose with an option to receive either 100 mg or 300 mg for subsequent dosing per clinician's discretion
‡ = Not included in total unique subjects exposed to SUBLOCADE, already accounted for in Study 13-0001 section of table

The table below illustrates the range of exposures in Phase 3.

Table 10 Cumulative treatment exposure by weeks in Phase 3 studies

	13-0001 (Phase 3 DB)			13-0003 (Phase 3 OL)				
				Roll-over			De novo	All Phase 3 (13-0001 & 13-0003)
Exposure	RBP-6000 300/100 (N=203)	RBP-6000 300/300 (N=201)	PBO (N=100)	RBP-6000 100→ RBP-6000 300/Flex (N=112)	RBP-6000 300→ RBP-6000 300/Flex (N=113)	PBO→ RBP-6000 300/Flex (N=32)	RBP-6000 300/Flex (N=412)	Total* RBP-6000 (N=848)
Duration of Exposure (Cumulative categories; Weeks), n (%)								
>= 4 Weeks	203 (100)	201 (100)	100 (100)	112 (100)	113 (100)	32 (100)	412 (100)	848 (100)
>= 8 Weeks	171 (84.2)	171 (85.1)	57 (57.0)	110 (98.2)	105 (92.9)	29 (90.6)	359 (87.1)	730 (86.1)
>=12 Weeks	157 (77.3)	157 (78.1)	50 (50.0)	105 (93.8)	100 (88.5)	28 (87.5)	338 (82.0)	680 (80.2)
>=16 Weeks	150 (73.9)	144 (71.6)	42 (42.0)	100 (89.3)	93 (82.3)	26 (81.3)	309 (75.0)	629 (74.2)
>=20 Weeks	137 (67.5)	132 (65.7)	39 (39.0)	96 (85.7)	86 (76.1)	26 (81.3)	293 (71.1)	588 (69.3)
>=24 Weeks	75 (36.9)	97 (48.3)	26 (26.0)	65 (58.0)	63 (55.8)	16 (50.0)	278 (67.5)	542 (63.9)
>=28 Weeks	1 (0.5)	0	0	0	1 (0.9)	0	260 (63.1)	485 (57.2)
>=32 Weeks	0	0	0	0	0	0	248 (60.2)	466 (55.0)
>=36 Weeks	0	0	0	0	0	0	243 (59.0)	450 (53.1)
>=40 Weeks	0	0	0	0	0	0	233 (56.6)	427 (50.4)
>=44 Weeks	0	0	0	0	0	0	228 (55.3)	412 (48.6)
>=48 Weeks	0	0	0	0	0	0	187 (45.4)	320 (37.7)

The extent of exposure, nature and frequency of safety monitoring were adequate to characterize the safety profile.

Most subjects in the study were white males with an average age of approximately 40 years old. About 10-20% were Hepatitis C seropositive at baseline. Approximately 50% of subjects had normal BMI (18.5-25), 30% of subjects were overweight (BMI:25-30) and 20 % of subjects were obese (BMI ≥30) in Phase 3 studies. The RBP-6000 300/300 group had the highest percentage of obese subjects (28%) compared with other groups. Per the Applicant, the impact of BMI on drug absorption is minimal.

9.1 Deaths

One death was reported in the clinical program. A 39-year-old male subject in Study 13-001 was found deceased from a gunshot wound nineteen days after the second injection. Police ruled the case a homicide; there were no factors suggesting a causal link to the study drug.

9.2 Serious Adverse Events

A total of 75 non-fatal SAEs occurred among 65 subjects across seven studies. None were related to injection site reactions. Accidental overdose was reported in two patients in the OL study and one patient on placebo in the double-blind study. Dr. Deng reviewed the case narratives and determined that most did not appear to be related to study drug. She carefully reviewed three cases of abnormal liver function tests that were classified as SAEs and identified alternative etiologies, including viral hepatitis.

9.3 Dropouts and/or Dose Reductions Due to Adverse Effects

In the Phase 3 data, the percentage of subjects with TEAEs leading to drug

discontinuation was higher in the Sublocade 300/300 mg group (5 %) than the Sublocade 300/100 group (3%), the Sublocade 300/Flex group (3-4%) and the placebo group (2%).

Patients on the higher-dose regimen most commonly dropped out due to drug-related effects such as elevated liver enzymes, sedation, somnolence, injection site ulcers, and nausea. Patients in other groups withdrew for drug-related reasons (injection site reactions, sedation, somnolence, constipation), but also for drug withdrawal syndrome.

In the Phase 3 open-label study (13-0003), patients were treated initially with 300 mg/month and then the dose could be adjusted at the clinician's discretion. Over the course of the study, 201 (30%) subjects had their dose reduced from 300 mg to 100 mg.

Among them, 49 (7.3%) subjects required dose reduction from 300 mg to 100 mg due to adverse events, including abnormal liver function tests, sedation, constipation, nausea, fatigue and headache. Upon Agency request, the Applicant clarified reasons for treatment dose reductions for other 152 subjects, noting that 72 were at patient's request, 68 at were PI's decision "as patient was doing well," and 12 were "at PI's discretion" for reasons that primarily involved adverse events (injection site reactions, constipation, LFT changes, nausea). This suggests the rate of dose reductions due to AEs was approximately 9%.

9.4 Significant Adverse Effects

9.4.1 Hepatic

Hepatic effects are a known risk of buprenorphine. Hepatic effects were reviewed through laboratory assessments and adverse events. Mild hepatic enzyme abnormalities were fairly common, but the more extreme elevations appeared to be dose-related.

Overall, a higher percentage of subjects in the RBP-6000 treatment groups had LFT values (ALT and AST) greater than 2 X ULN post-baseline than in the placebo group. Furthermore, percentage of subjects with LFT values greater than 3 x ULN was higher in the high dose regimens RBP-6000 300/300 mg (ALT: 12.44%, AST: 11.44%) compared with low dose regimen RBP-6000 300/100 mg (ALT: 5.42%, AST: 7.88%). It is not known how this compares to transmucosal buprenorphine treatment.

The hepatic-related adverse events were almost entirely laboratory value-related. No Hy's law case was identified in the clinical development program. Three SAEs of hepatic injuries were reported in the pooled Phase 1 studies after single dose exposure at 100 mg, 200 mg and 300 mg (Low molecular weight). One subject had newly diagnosed hepatitis C after the drug exposure, one subject had preexisting hepatitis C and B, and one subject had elevated Alkaline Phosphatase level. Therefore, all these three cases do not meet the Hy's law criteria of lacking alternative etiologies.

In the controlled study, a total of 5 (2.5%) TEAEs of hepatic injury resulted in drug discontinuation in the RBP 6000 300/300 mg group vs 0 TEAEs in the RBP-6000 300/100 mg

group and the placebo group. A total of 15 (4%) TEAEs of hepatic injuries leading to drug reduction and drug discontinuation were reported in the *de novo* 300/Flex group.

9.4.2 Cardiac

A Customized MedDRA Query (CMQ) regarding cardiac disorder was performed in pooled Phase 3 studies, including cardiac arrhythmia and reported abnormal EKG findings. Overall, TEAEs of cardiac disorder were rarely reported and evenly distributed across groups. A few cases of mild to moderate QT prolongation were reported in the RBP-6000 treatment group which were considered non-clinically significant. These findings are consistent with the EKG findings from the QT-IRT team.

9.4.3 Pancreatic

Because of findings in the pre-clinical program, the safety data were explored to determine whether there was a signal for pancreatic adverse effects. A Standardized MedDRA Query (SMQ) revealed that nonspecific symptoms such as nausea, vomiting were frequently reported in both placebo group and RBP-6000 treatment groups, but very few cases reported pancreatic enzymes increased (amylase, trypsin and lipase). TEAEs related to pancreatic enzymes increased were evenly distributed between placebo group and RBP-6000 treatment group.

9.4.4 Injection Site

Most injection site reactions were of mild to moderate severity, with one report of severe injection site pruritus. None of the injection site reactions were serious. One reaction, an injection site ulcer, led to study treatment discontinuation. The table below, prepared by Dr. Deng, illustrates the frequency and types of injection site reactions.

Table 11 Injection Site Adverse Drug Reactions Reported by ≥ 2 Subjects in the Phase 3 Double-Blind Study

PT, n (%)	13-0001 (Ph3DB)			13-0003 (Ph3OL)				All Phase 3
				Roll–over[6]			De-novo	
	SUBLOCADE 300/300 (N = 201)	SUBLOCADE 300/100 (N = 203)	PLA (N = 100)	SUBLOCADE 300 → SUBLOCADE 300/Flex (N=113)	SUBLOCADE 100 → SUBLOCADE 300/Flex (N=112)	Placebo → SUBLOCADE 300/Flex (N=32)	SUBLOCADE 300/Flex (N=412)	Total SUBLOCADE (N=848)
Subjects with any TEAE	38 (18.9%)	28 (13.8%)	9 (9.0%)	6 (5.3%)	13 (11.6%)	2 (6.3%)	61 (14.8%)	140 (16.5%)
Injection site pain	12 (6.0%)	10 (4.9%)	3 (3.0%)	4 (3.5%)	2 (1.8%)	2 (6.3%)	33 (8.0%)	61 (7.2%)
Injection site pruritus	19 (9.5%)	13 (6.4%)	4 (4.0%)	2 (1.8%)	6 (5.4%)	1 (3.1%)	17 (4.1%)	56 (6.6%)
Injection site erythema	6 (3.0%)	9 (4.4%)	0	1 (0.9%)	4 (3.6%)	0	21 (5.1%)	40 (4.7%)
Injection site induration	2 (1.0%)	2 (1.0%)	0	0	1 (0.9%)	0	7 (1.7%)	12 (1.4%)
Injection site bruising	2 (1.0%)	2 (1.0%)	0	0	0	0	2 (0.5%)	6 (0.7%)
Injection site swelling	1 (0.5%)	2 (1.0%)	0	1 (0.9%)	1 (0.9%)	0	1 (0.2%)	6 (0.7%)
Injection site discomfort	1 (0.5%)	1 (0.5%)	0	0	0	0	3 (0.7%)	5 (0.6%)
Injection site reaction	1 (0.5%)	0	0	0	3 (2.7%)	0	1 (0.2%)	5 (0.6%)
Injection site cellulitis	0	1 (0.5%)	0	0	0	0	2 (0.5%)	3 (0.4%)
Injection site infection	1 (0.5%)	0	1 (1.0%)	0	0	0	2 (0.5%)	3 (0.4%)

[6] Both Roll-over and De-novo patients received Suboxone films for a two-week run-in period before they switched to Sublocade injections.

9.4.5 CNS Depression

In the Ph3DB study, TEAEs potentially associated with CNS depression were observed at a higher percentage in the Sublocade 300/100 mg group (11.8%) than in the 300/300 mg group (7.0%) and the placebo group (4.0%). In the Ph3OL study, the percentages of subjects with reports of these TEAEs ranged from 7% to 8 % across subject groups.

In the Ph3DB study one SAE, accidental overdose in one subject (Subject 028-0031) in the PBO group, was possibly related to CNS depression. Three subjects discontinued study treatment due to events potentially pertaining to CNS depression: two subjects with sedation (one each in the 300/100 mg [Subject 016-0085] and 300/300 mg groups [Subject 001-0005]) and one subject with somnolence in the 300/300 mg group (Subject 028-0041).

In the Ph3OL study, five subjects had SAEs potentially associated with CNS depression (accidental overdose [de novo Subjects 028-9020 and 048-9039]; road traffic accident [de novo Subject 040-9007]; dizziness [de novo Subject 048-9045]; and generalized tonic-clonic seizure [roll-over Subject 028-0036]). Two subjects in the de novo 300 mg group discontinued study treatment due to events potentially pertaining to CNS depression: accidental overdose (Subject 048-9039] and somnolence (Subject 042-9033). One subject in the roll-over group discontinued study treatment due to sedation (Subject 034-0023).

No TEAEs potentially associated with respiratory depression were reported in any RBP-6000 study.

9.5 Common AEs

The systemic safety profile for SUBLOCADE, given by a HCP in clinical trials, was consistent with the known safety profile of transmucosal buprenorphine. Common adverse reaction associated with buprenorphine included constipation, nausea, vomiting, abnormal liver enzymes, headache, sedation and somnolence. Dose-dependent hepatic effects observed in the Phase 3, double-blind study (13-0001, NCT02357901) included the incidence of ALT more than 3 times the upper limit of normal (> 3 × ULN) in 12.4%, 5.4%, and 4.0% of the Sublocade 300/300-mg, Sublocade 300/100-mg, and placebo groups, respectively. The incidence of AST > 3 × ULN was 11.4%, 7.9%, and 1.0%, respectively. The most commonly-reported adverse events, apart from injection-site reactions, are shown in Table 12, prepared by Dr. Deng.

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Table 12 Adverse Reactions for Phase 3 Double-Blind Study: ≥2% of Subjects Receiving SUBLOCADE

System Organ Class Preferred Term	PLACEBO	Sublocade 300/100 mg	Sublocade 300/300 mg
	Count (%)	Count (%)	Count (%)
Total	N=100	N=203	N=201
Gastrointestinal disorders	12(12%)	51(25.1%)	45(22.4%)
Constipation		19 (9.4)	16 (8)
Nausea	5 (5)	18 (8.9)	16 (8)
Vomiting	4 (4)	19 (9.4)	11 (5.5)
General disorders and administration site conditions	17(17%)	40(19.7%)	49(24.4%)
Fatigue	3 (3)	8 (3.9)	12 (6)
Investigations	2(2%)	21(10.3%)	19(9.5%)
Alanine aminotransferase increased		2 (1)	10 (5)
Aspartate aminotransferase increased		7 (3.4)	9 (4.5)
Blood creatine phosphokinase increased	1 (1)	11 (5.4)	5 (2.5)
Gamma-glutamyl transferase increased	1 (1)	6 (3)	8 (4)
Nervous system disorders	7(7%)	35(17.2%)	25(12.4%)
Headache	6 (6)	19 (9.4)	17 (8.5)
Sedation		7 (3.4)	3 (1.5)
Somnolence		10 (4.9)	4 (2)

*Includes elevations of ALT, AST, GGT, and/or bilirubin. There were no cases of severe drug-induced liver injury.

9.6 Safety Analyses by Demographic Subgroups

Safety analysis was performed by age, sex, race and ethnic subgroup in Phase 3 DB study (13-0001) and Phase 3 OL study (13-0003). It appears that female subjects reported TEAE related to GI disorders, general disorders, injection site reactions more frequently compared with male subjects. No other demographic interactions were observed.

9.7 Other Safety Concerns

Certain concerns not observed in the clinical trials may arise in the post-market setting. These involve the potential for severe consequences if the product is injected intravenously, and the possibility of severe precipitated withdrawal if the product is initiated in a patient still dependent on a full agonist.

9.7.1 Precipitated Withdrawal

Buprenorphine itself can precipitate withdrawal if initiated in patients who are not yet in significant opioid withdrawal. For this reason, initial dosing is generally cautious and typically begins with a dose of 2 mg- 4 mg. Sublocade contains a high dose of buprenorphine. The clinical trials included a significant period of dose run-in on transmucosal buprenorphine. It is not known whether Sublocade could precipitate withdrawal if initiated in patients who have not had a period of transmucosal buprenorphine treatment.

9.7.2 Consequences of Intravenous Injection

Sublocade was administered in a supervised setting by HCPs in the clinical development program. If a patient, household contact, or associate were to obtain access to Sublocade, the pre-filled syringe containing a Schedule III opioid might be an attractive target for abuse by the i.v. route. As noted above, it is predicted that contact with blood would result in the formation of a solid, with resulting occlusion and possibly tissue damage or embolus.

10 Advisory Committee Meeting

A Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting was held on October 31, 2017 to discuss NDA 209819, RBP-6000 (Buprenorphine -ATRIGEL monthly depot) and its safety and efficacy for the proposed indication of maintenance treatment of opioid dependence. Voting participants included members of both committees, as well as Special Government Employees with expertise in addiction medicine designated as temporary voting members.

The following specific discussion topics and voting questions were posed to the committee for deliberation:

1. VOTE: Do the data from the clinical trial, taken together with the results of the blockade study, provide substantial evidence of effectiveness of RBP-6000 for the treatment of opioid use disorder in patients who had undergone induction with a transmucosal buprenorphine product?

   Yes: 17 No: 2 Abstain: 0

2. VOTE: Do the provided safety data sufficiently support the use of the proposed RBP 300 mg/300 mg dose regimen, given that the steady-state plasma exposures associated with RBP-6000 300 mg exceed those associated with the highest labeled dose of the reference product, Subutex?

   Yes: 13 No: 6 Abstain: 0

3. DISCUSSION: Discuss the role of the RBP-6000 300/300 mg regimen, given the similarity in efficacy results between the RBP-6000 300/300 mg and RBP-6000 300/100 mg.

   There was extensive discussion about the role of the RBP-6000 300/300 mg regimen,

noting that some dose-dependent adverse effects were observed without clear incremental benefit. It was noted that there were some data to suggest that some patients, such as injection drug users, might require higher buprenorphine exposures for effective treatment, but convincing evidence of benefit was lacking. The Committee recommended studies be performed post-marketing to define the population that would benefit from the high dosing regimen 300/300 mg.

4. DISCUSSION: Discuss the pros and cons of the restricted distribution under a Risk Evaluation and Mitigation Strategy (REMS), as proposed by the Applicant, to mitigate the risks that might ensue from direct distribution of RBP-6000 to patients.

   a. What barriers to access may arise from implementing a restricted distribution system?
   b. What systemic or institutional barriers might be anticipated for a restricted distribution system?
   c. What modifications might address barriers to access while mitigating risk?
   d. Is the proposed REMS sufficient, or are other measures needed?

The Committee also agreed that an appropriate REMS needs to be implemented to prevent the product from being in the hands of the patient prior to administration. Although some concerns were voiced about how the proposed distribution system would be implemented in specific settings, no participants objected to the idea of restricted distribution; most clearly endorsed its importance.

5. VOTE: Do you recommend approval of this application?

   Yes: 18 No: 1 Abstain: 0

The Advisory Committee panel members recommended approval as a majority, although not unanimously.

The Committee also noted that clinical data of surgical removal of the RBP-6000 in case of medical emergency was lacking. They wanted to know how long the buprenorphine level will be detectable after the last injection of RBP-6000. The Committee recommended that the instructions for surgical removal of RBP-6000 should be addressed in the labeling.

11 Pediatrics

Indivior received Orphan Designation for buprenorphine used in the treatment of opioid dependence. Therefore, the application is exempt from the requirements of the Pediatric Research Equity Act.

Additionally, waivers of PREA requirements have previously been issued to other sponsors of buprenorphine products to treat opioid dependence on the basis of infeasibility. The prevalence of OUD in the pre-adolescent population is very low, and this product would not be suitable

for treating iatrogenic opioid dependence (i.e., physical dependence without meeting criteria for OUD). Prevalence in adolescents under age 17 is also too low for feasible study.

12 Other Relevant Regulatory Issues

Review of financial disclosures revealed no concerns.
Three sites for Study 13-0001, as well as the single site for the opioid blockade study were selected for inspection. OSI reviewer Dr. Damon Green concluded that the studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

13 Labeling

The submitted proposed labeling is in Physician's Labeling Rule (PLR) format. The approved labeling for Suboxone/Subutex tablets forms the foundation for RBP-6000 labeling, with new information related to the novel delivery system and the clinical trials, included throughout in relevant sections.

The following are recommendations for the labeling.

- INDICATION AND USAGE

Indivior proposed the following indication statement:

RBP-6000 is indicated for the 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 and should be used as part of a complete treatment program that includes counseling and psychosocial support.

The Division recommends modifying the language to reflect the fact that study participants had to be dose-stabilized for at least seven days before initiating Sublocade.

- DOSAGE AND ADMINISTRATION

Indivior proposed the following:
The recommended dosing regimen for RBP-6000 is 300 mg monthly for the first 2 months followed by maintenance treatment of 100 mg or 300 mg monthly based on the clinical condition of the patient.

The Division recommends modifying the language so that the 300 mg/100 mg regimen is recommended for all patients. Increase of the maintenance dose to 300 mg/month would be reserved only for patients not responding to the lower dose.

- WARNINGS AND PRECAUTIONS

Compared with current Suboxone labeling, the proposed label lacked the following information, which will be added:

(b) (4)

14 Postmarketing Recommendations

14.1 Risk Evaluation and Mitigation Strategies (REMS)

The Risk Evaluation and Mitigation Strategy proposed by Indivior was reviewed by the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology. DRISK has determined that a REMS with elements to assure safe use (ETASU) is needed to ensure the benefits of Sublocade outweigh its risks. The REMS should include restricted distribution with Sublocade only being dispensed in healthcare settings that are certified. (b) (4)

Currently, all buprenorphine products indicated for MAT of OUD are approved with REMS (Suboxone/Subutex REMS, the shared system Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS and the Probuphine REMS). As an injectable depot, Sublocade differs significantly from the oral transmucosal formulations of buprenorphine. Those products are self-administered by patients in their homes and the REMS are designed to mitigate risks associated with accidental overdose, particularly in children as well as misuse, and abuse. This is in contrast to Sublocade which was designed to be administered by a HCP. Probuphine was similarly designed to be administered by HCP, but carries different risks as it is an implant device.

The REMS for transmucosal buprenorphine products for MAT consist of a Medication Guide and ETASU (i.e., safe use conditions and monitoring) which are not linked to distribution and therefore is not restrictive program. The REMS for these products were required to address an increase in accidental exposures to children, increased misuse and abuse, as well as to improve prescribing practices of these products.

The goal of the Probuphine REMS is to mitigate the risk of complications of migration, protrusion, expulsion and nerve damage associated with insertion and removal of Probuphine and the risks of accidental overdose, misuse and abuse if the implant comes out of the skin. The Probuphine REMS consists of a Medication Guide and the ETASU that are comprised requirements that are restrictive and include healthcare provider (HCP) certification (e.g., HCP that prescribes and/or inserts Probuphine must be certified) and patient monitoring for removal of Probuphine. There are corresponding REMS materials for HCP education, enrollment, logging of insertion and removal procedures and patient education. The training with this REMS is linked to the ability to prescriber, insert and remove Probuphine.

The risks of Sublocade when injected subcutaneously have been reasonably well-characterized. During the clinical development period, Sublocade was administered by a HCP and the Applicant has included this in their labeling. Sublocade was not studied or evaluated for take-home use or self-administration by patients. However, once marketed, there is concern that there is potential for intravenous administration, because the product will be available in a prefilled syringe with a needle attached, which may be attractive to patients with a history of IV drug abuse, their household contacts, and associates.

The Applicant provided *in vitro* assay data showing that when Sublocade was injected in a tube containing dog blood, immediate clogging occurred. Based on the *in vitro* tube assay results, it is likely that an occlusion would form due to rapid solidification of the formulation when placed in aqueous fluid. Other potential downstream adverse events (AEs) that may result from IV injection (i.e. tissue damage, embolus, rapid dissolution resulting in high levels of opioid and respiratory depression).

The Applicant has proposed "Dosage and Administration" labeling language that states that this product is for subcutaneous injection only and that it "should only be prepared and administered by a healthcare provider." They also have a "Warning and Precaution" for

(b) (4)

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The Applicant proposed a

(b) (4)

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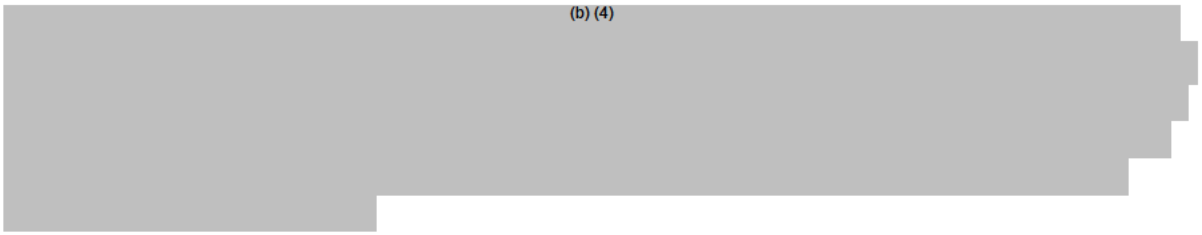
However, DRISK noted that a more appropriate goal would be:

The goal of the REMS is to mitigate the risk of serious harm or death with intravenous self-administration by:

- *Ensuring healthcare settings and pharmacies are certified and only dispense Sublocade directly to a health care provider for administration by a healthcare provider*



DRISK conducted several interviews with healthcare providers and administrators in various health care settings to gain insight into the diversity of systems and approaches. DRISK noted that in some healthcare settings there is a centralized pharmacy for inpatient and outpatient and other systems may have use a separate pathway for procurement of drugs for outpatient pharmacies. The Agency has determined that all sites receiving product from the distributor should be certified and enrolled to ensure that in each case, in the various healthcare settings, there will be processes and procedures in place to ensure that dispensing staff are aware Sublocade should be administered by a HCP and cannot be given directly to patients.

To assist health care providers with understanding the requirements of the REMS, the Agency is requiring a Fact Sheet that explains how to obtain Sublocade for their patients, enrollment forms, and letters to healthcare professionals.

The following materials are part of the Sublocade REMS:
Enrollment Forms:

Healthcare Setting and Pharmacy:

5. Healthcare Setting and Pharmacy Enrollment Form

Communication Materials

6. Dear Healthcare Provider REMS Letter
7. Fact Sheet

Other Materials

8. REMS Program Website

14.2 Postmarketing Requirements (PMRs) and Commitments (PMCs)

In addition to certain post-marketing preclinical studies, it is recommended that the Indivior be required to conduct two clinical trials and to commit to certain pharmacokinetic analyses to further elucidate the safe and effective clinical use of Sublocade.

1. As noted above some dose-dependent adverse events (elevated hepatic enzymes, GI symptoms) were noted, while dose-dependent incremental efficacy was not demonstrated for the study population as a whole. However, some subset analyses suggested that there could be sub-populations (e.g., intravenous drug abusers) who may benefit from the higher dose regimen. Identifying these subpopulations, and providing patient selection guidance to clinicians on when the risks of the higher dose regimen are likely to be outweighed by benefits, would contribute to safer use of the drug.
2. The clinical trial was conducted in patients who initiated treatment with sublingual buprenorphine/naloxone (SL BPN), and then tolerated and completed an initial open-label run-in with SL BPN. In the current medical climate, there is great interest in initiating treatment using a depot formulation as rapidly as possible, increasing the likelihood of the patient adherence to treatment from the outset, and reducing the need to provide take-home SL BPN medication for outpatient use. It is, therefore, anticipated that clinicians may elect to accelerate the initiation of Sublocade treatment by omitting some or all of the SL BPN titration period. However, because the doses of buprenorphine provided by Sublocade are higher than doses of SL BPN typically used to initiate treatment, there is a risk that precipitated withdrawal, a clinically serious condition, could occur if Sublocade is initiated without a period of SL BPN titration. Further information on how Sublocade could be initiated without SL BPN titration would contribute to safer use of the drug.
3. The clinical pharmacology modeling suggests that Sublocade might be effective when given at dosing intervals less frequent than monthly. This might be addressed through pharmacokinetic studies and modeling.
4. A greater understanding of how to transfer patients who are already clinically stable (vs. new entrants to treatment who are briefly dose-stabilized) onto Sublocade would also contribute to safer use of the drug. For example, patients already clinically stable on 8 mg/day of Suboxone might not require the loading doses of 300 mg/month. This might also be addressed through pharmacokinetic studies and modeling.

Enhanced pharmacovigilance for a period of 3 years will also be required. Indivior will be asked to submit as expedited (15-day) reports all initial and follow-up reports of:

1. known or suspected intravenous administration of Sublocade, regardless of outcome (serious or non-serious) and whether the product was self-administered or involved inadvertent intravenous administration by health care professionals
2. surgical removal of the Sublocade depot and any post-removal complications

The pharmacology/toxicology review team identified the following additional issues to be explored post-marketing:

1. Conduct a fertility and early embryonic development study testing N-methyl-pyrrolidone in the rat model.

2. Conduct an embryofetal development study testing N-methyl-pyrrolidone in the rat model.

3. Conduct an embryofetal development study testing N-methyl-pyrrolidone in the rabbit model.

4. Conduct a pre- and post-natal development study testing N-methyl-pyrrolidone in the rat model.

5. Conduct a mode of action assessment for N-methyl-pyrrolidone-induced mouse hepatocellular adenomas and carcinomas to inform the human risk assessment for NMP.

APPENDIX
Time-and-events Tables for Study 13-0001

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Table 4 Schedule of Events: Screening and SUBOXONE Sublingual Film Induction

Evaluation	Screening (2 weeks)	SUBOXONE Sublingual Film Run-in						
		Induction (3 days)			Dose Adjustment (4-11 days)			
	Days -30 to -15	Day -14	Day -13	Day -12	Day -11	Day -8	Day -4	Day -1
						+ 1 day	± 1 day	-1 day
Informed Consent	X							
Inclusion/Exclusion Criteria Reviewed	X							
IXRS	X							
Demographics	X							
Medical History[1]	X							
eC-SSRS (Baseline Version)	X							
Physical Examination[2]	X							
Vital Signs[3]	X	X	X	X	X	X	X	X
Body Weight	X							
BMI Calculation	X							
Hip-to-Waist Ratio	X							
12-lead ECG (supine ≥ 10 min, triplicate recording at screening only)	X					X[16]		
UDS	X[4, 5]							
Urine Pregnancy Test[6]		X						
Screening Labs/Hormone Panel	X							
Urinalysis/Haematology/Serum Chemistry	X							
Opioid Craving VAS[7]	X					X	X	X
COWS[7]	X	X	X	X	X	X	X	X
SOWS[7]	X	X	X	X	X	X	X	X
TLFB Interview	X							

Evaluation	Screening (2 weeks)	SUBOXONE Sublingual Film Run-in						
		Induction (3 days)			Dose Adjustment (4-11 days)			
	Days -30 to -15	Day -14	Day -13	Day -12	Day -11	Day -8	Day -4	Day -1
						+ 1 day	± 1 day	-1 day
CGI-S	X							
BDI-II	X							
BPI-Short Form	X							
Concomitant Medications	X[8]	X	X	X	X	X	X	X
AE Assessment[9]	X	X	X	X	X	X	X	X
Day -1 Criteria Reviewed						X[10]	X[10]	X[11]
PK Sampling[12]							X[12]	
SUBOXONE sublingual film administration[13]		X[14]	X	X	X	X[15]	X[15]	X[15]
EQ-5D-5L	X					X		
SF-36v2	X					X		
Employment Status and Health Insurance	X					X		
HCRU	X							

AE = adverse event; BDI-II = Beck Depression Inventory-II; BMI = body mass index; BPI = Brief Pain Inventory; CGI-S = Clinical Global Impression-Severity; COWS = Clinical Opiate Withdrawal Scale; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; HCRU = healthcare resource utilization; IXRS=Interactive Voice/Web Response System; PK = pharmacokinetic/pharmacokinetics; SAE = serious adverse event; SF-36v2 = 36-Item Short Form Health Survey, Version 2; SOWS = subjective opiate withdrawal scale; TLFB = Timeline Followback; UDS = Urine Drug Screen; VAS = Visual Analog Scale

1. Medical and psychiatric history, including use of tobacco, drugs of abuse, alcohol and caffeine.
2. Complete examination (excluding pelvic, breast and rectal), including general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities and a brief neurological assessment.
3. Included blood pressure (BP; supine ≥ 3 minutes), pulse oximetry, pulse rate, respiratory rate, oral temperature and height (screening visit only). Vital signs were assessed within 60 minutes before administration of SUBOXONE sublingual film.
4. Buprenorphine was included in the UDS at screening only. If, after discussion with the subject, the investigator had reason to believe a positive UDS for buprenorphine may have been due to a false-positive test result, a 1-time retest was allowed. This retest must have been performed within 48 hours of receipt of the initial buprenorphine UDS test result.
5. Additional unscheduled screens may have been performed if abuse was suspected.

6. Only for female subjects who were of childbearing potential (not postmenopausal or surgically sterile for at least 1 year).
7. Assessments should have been performed prior to each SUBOXONE sublingual film dosing and at approximately the same time each day (± 2 hours).
8. Included a review of previous (within 30 days prior to screening) and ongoing medications.
9. A PK sample was to be taken as soon as possible after any SAE was reported. If possible, an additional sample should have been collected when the SAE had resolved.
10. This visit became Day -1 if the following criteria were met:
    - no allergic reaction to SUBOXONE sublingual film
    - daily dose of SUBOXONE sublingual film between 8 mg/2 mg to 24 mg/6 mg (inclusive) buprenorphine/naloxone
    - a COWS score of ≤ 12
    - an Opioid Craving VAS score of ≤ 20 mm

    If Day -1 criteria were met, the subject was scheduled the following day (Injection Visit #1/Day 1) to receive the first injection of study treatment after randomisation criteria were met.
11. If Day -1 criteria were not met after 14 days of SUBOXONE sublingual film treatment and a subject still had significant withdrawal signs/symptoms and opioid cravings (COWS score > 12 and Opioid Craving VAS > 20 mm), they were not eligible to continue in the study. They were provided with information on the options for opioid use disorder treatment.
12. Blood sampling for PK assessments started on Day -1 in subjects who met Day -1 criteria. See PK table (see Appendix 4 of the protocol in Appendix 16.1.1) for exact time points. A resting 12-lead ECG was taken ≤ 60 minutes prior to the first PK sample collected on Day -1.
13. SUBOXONE sublingual film dosing should have taken place at the same time of day (± 2 hours).
14. Subjects should have been in opioid withdrawal (COWS score > 12) prior to receiving the first dose of SUBOXONE sublingual film on Day -14.
15. Subjects should **not** have taken their dose of SUBOXONE sublingual film until after it had been determined if they had met Day -1 criteria (see footnote #10 for specific criteria).
16. Performed only on Day -1.

Table 5 Schedule of Events: RBP-6000 Injection Visits 1–3

Evaluation	Inj 1	Postinjection 1 Assessments							Inj 2	Postinjection 2 Assessments				Inj 3	Postinjection 3 Assessments			
	Wk1 D 1	Wk1 D 2	Wk1 D 3*	Wk1 D 4*	Wk1 D 5*	Wk2 D 8	Wk3 D 15	Wk4 D 22	Wk5 D 29	Wk5 D 30	Wk6 D 36	Wk7 D 43	Wk8 D 50	Wk9 D 57	Wk9 D 58	Wk10 D 64	W11 D 71	Wk12 D 78
Window		+1	NA	NA	NA	±1	±1	±1	±2	+1	±1	±1	±1	±2	+1	±1	±1	±1
IXRS	X								X					X				
Randomisation	X																	
Vital Signs[1]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight	X																	
BMI Calculation	X																	
Hip-to-Waist Ratio	X																	
12-lead ECG (supine ≥ 10 min)[2]						X	X	X			X	X	X			X	X	X
4-hr Continuous Pulse Oximetry[3]	X								X					X				
Holter (24-hour) Monitor Recording[4]	X	X							X	X				X	X			
Haematology/ Serum Chemistry[5]	X						X		X			X		X			X	
Hormone Panel	X																	
Urinalysis[5]	X						X		X			X		X			X	
Urine Pregnancy Test[6]	X						X		X			X		X			X	
UDS[5,7]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X
PK Sampling[8]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X
PGx Sampling[9]	X																	
Concomitant Medications	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment[10]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X

Evaluation	Inj 1	Postinjection 1 Assessments							Inj 2	Postinjection 2 Assessments				Inj 3	Postinjection 3 Assessments			
	Wk1 D 1	Wk1 D 2	Wk1 D 3*	Wk1 D 4*	Wk1 D 5*	Wk2 D 8	Wk3 D 15	Wk4 D 22	Wk5 D 29	Wk5 D 30	Wk6 D 36	Wk7 D 43	Wk8 D 50	Wk9 D 57	Wk9 D 58	Wk10 D 64	W11 D 71	Wk12 D 78
Window		+1	NA	NA	NA	±1	±1	±1	±2	+1	±1	±1	±1	±2	+1	±1	±1	±1
eC-SSRS (Since last-visit-version)[11]	X					X	X	X	X		X	X	X	X		X	X	X
TLFB Interview[11]	X					X	X	X	X		X	X	X	X		X	X	X
Opioid Craving VAS[11]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X
COWS[11]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X
SOWS[11]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S[11]	X								X					X				
CGI-I[11]	X								X					X				
BDI-II[11]	X								X					X				
BPI[11]	X								X					X				
Study Treatment Injection	X								X					X				
SUBOXONE Sublingual Film Taper[12]	X	X	X	X	X													
Injection Site Grading Scale[13]	X	X							X	X				X	X			
Injection Site Pain VAS[14]	X								X					X				
Injection Site Evaluation[15]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X
Behavioural Therapy[16]	X					X	X	X	X		X	X	X	X		X	X	X
EQ-5D-5L	X[17]													X[17]				
SF-36v2	X[17]													X[17]				
MSQ														X[17]				

Evaluation	Inj 1	Postinjection 1 Assessments							Inj 2	Postinjection 2 Assessments				Inj 3	Postinjection 3 Assessments			
	Wk1 D 1	Wk1 D 2	Wk1 D 3*	Wk1 D 4*	Wk1 D 5*	Wk2 D 8	Wk3 D 15	Wk4 D 22	Wk5 D 29	Wk5 D 30	Wk6 D 36	Wk7 D 43	Wk8 D 50	Wk9 D 57	Wk9 D 58	Wk10 D 64	W11 D 71	Wk12 D 78
Window		+1	NA	NA	NA	±1	±1	±1	±2	+1	±1	±1	±1	±2	+1	±1	±1	±1
Employment Status and Health Insurance	X[17]								X[17]					X[17]				
HCRU	X[17]								X[17]					X[17]				

AE = adverse event; BDI-II = Beck Depression Inventory-II; BMI = body mass index; BPI = Brief Pain Inventory; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; COWS = Clinical Opiate Withdrawal Scale; D = Day; ECG = electrocardiogram; eCRF = electronic case report form; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; HCRU = healthcare resource utilization; Inj = injection; IXRS=Interactive Voice/Web Response System; MSQ = Medication Satisfaction Questionnaire; NA = not applicable; PGx = Pharmacogenomic; PK = pharmacokinetic/pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; SF-36v2 = 36-Item Short Form Health Survey, Version 2; SOWS = subjective opiate withdrawal scale; TLFB = Timeline Followback; UDS = urine drug screen; VAS = Visual Analog Scale; Wk = Week

1. Included blood pressure (BP; supine ≥ 3 minutes), pulse oximetry, pulse rate, respiratory rate and oral temperature. Vital signs on injection days were taken ≤ 60 minutes prior to SC injection and then 0.5, 2 and 4 hours post SC injection (± 15 minutes).
2. A resting 12-lead ECG was taken ≤ 1 hour prior to each PK sample collection.
3. Pulse oximetry was measured from at least 30 minutes prior to SC injection through at least 4 hours postinjection. Results obtained within 30 minutes preinjection and 4 hours postinjection (± 15 minutes) were recorded in the eCRF.
4. Holter monitor recording was obtained from at least 30 minutes preinjection through at least 24 hours postinjection. The Holter monitor must have been applied prior to PK sample collection on injection days to allow an ECG extraction before PK collection.
5. Blood and urine samples were taken ≤ 60 minutes prior to SC injection.
6. Only for female subjects who were of childbearing potential (not postmenopausal or surgically sterile for at least 1 year).
7. An additional blinded UDS could have been done if use was suspected. Oxycodone may not have shown up in all opiate assays and should have been assessed separately. Prior to the study treatment injection, if the investigator was concerned about subject safety secondary to possible benzodiazepine use, an in-office benzodiazepine urine test may have been performed. If the test was positive, the investigator was to contact the medical monitor or the sponsor to discuss whether or not to administer the study treatment.
8. See PK table (see Appendix 4 of the protocol in Appendix 16.1.1) for exact time points.
9. Samples taken preinjection on Day 1. See PGx Sampling Schedule (see Appendix 5 of the protocol in Appendix 16.1.1) for exact time points.
10. A PK sample was to be taken as soon as possible after any SAE was reported. If possible, an additional sample should have been collected when the SAE had resolved.
11. Assessments should have been performed prior to study treatment injection and at approximately the same time each day ± 2 hours.
12. A SUBOXONE sublingual film taper was initiated for all subjects at the first injection visit (Day 1) after the 4-hour PK laboratory specimen had been obtained. The dosing regimen was as follows: Day 1, 6 mg; Day 2, 4 mg; Day 3, 4 mg; Day 4, 2 mg; and Day 5, 2 mg. On Day 2, the visit window of + 1 did NOT apply to the 4-mg dose of SUBOXONE sublingual film. If it was anticipated that the Day 2 visit window would be used, the 4-mg dose of

SUBOXONE sublingual film should have been given to the subject at the Day 1 visit for at-home dosing on the actual Day 2. Note that Day 3, Day 4 and Day 5 doses were taken at home. See Section 9.4.1.2 for additional details.

13. Local injection site grading was performed at the time of SC injection (within 10 minutes), 4 hours (± 30 minutes) and 24 hours (± 4 hours) post SC injection.
14. The injection site pain VAS scores were obtained (after the completion of the injection) within 1 minute and at 5, 10, 15, 30, 60 and 120 minutes (± 5 minutes). The timing of the injection site pain VAS should have been measured from the end of the injection.
15. Injection site was evaluated for evidence of attempted removal.
16. Subjects were to receive manual-guided, individual behavioural therapy at least once a week after randomisation.
17. Assessments should have been performed prior to study treatment injection.

***Not a clinic visit; take-home doses of SUBOXONE sublingual film were provided on Day 2 for Days 3, 4 and 5. If subjects were randomised but did not receive an injection of study treatment, they did not receive the SUBOXONE sublingual film taper and were terminated from the study.**

Table 6 Schedule of Events: RBP-6000 Injection Visits 4–6, End of Study/Early Termination Visit and Follow-up

Evaluation	Inj 4	Postinjection 4 Assessments				Inj 5	Postinjection 5 Assessments				Inj 6	Postinjection 6 Assessments				EOS/ET/ Safety Follow-up	
	Wk13 D 85	Wk13 D 86	Wk14 D 92	W15 D 99	Wk16 D 106	Wk17 D 113	Wk17 D 114	Wk18 D 120	Wk19 D 127	Wk20 D 134	Wk21 D 141	Wk21 D 142	Wk22 D 148	W23 D 155	Wk24 D 162	Wk25 D 169[17]	Wk29 D 197[18]
Window	±2	+1	±1	±1	±1	±2	+1	±1	±1	±1	±2	+1	±1	±1	±1	±2	±2
IXRS	X					X					X					X[19]	
Vital Signs[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight	X										X					X	
BMI Calculation	X										X					X	
Hip-to-Waist Ratio	X										X					X	
12-lead ECG (supine ≥ 10 min)[2]			X	X	X			X	X	X			X	X	X	X	X
4-hr Continuous Pulse Oximetry[3]	X					X					X						
Holter (24-hour) Monitor Recording[4]	X	X				X	X				X	X					
Haematology/Serum Chemistry[5]	X			X		X			X		X			X		X	X
Hormone Panel	X										X					X	
Urinalysis[5]	X			X		X			X		X			X		X	X
Urine Pregnancy Test[6]	X			X		X			X		X			X		X	
Serum Pregnancy Test[6]																	X
UDS[5,7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Sampling[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PGx Sampling[9]																X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Evaluation	Inj 4	Postinjection 4 Assessments				Inj 5	Postinjection 5 Assessments				Inj 6	Postinjection 6 Assessments				EOS/ET/ Safety Follow-up	
	Wk13 D 85	Wk13 D 86	Wk14 D 92	W15 D 99	Wk16 D 106	Wk17 D 113	Wk17 D 114	Wk18 D 120	Wk19 D 127	Wk20 D 134	Wk21 D 141	Wk21 D 142	Wk22 D 148	W23 D 155	Wk24 D 162	Wk25 D 169[17]	Wk29 D 197[18]
Window	±2	+1	±1	±1	±1	±2	+1	±1	±1	±1	±2	+1	±1	±1	±1	±2	±2
AE Assessment[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
eC-SSRS (Since last-visit-version)[11]	X		X	X	X	X		X	X	X	X		X	X	X	X	
TLFB Interview[11]	X		X	X	X	X		X	X	X	X		X	X	X	X	X
Opioid Craving VAS[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
COWS[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SOWS[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CGI-S[11]	X					X					X					X	
CGI-I[11]	X					X					X					X	
BDI-II[11]	X					X					X					X	
BPI[11]	X					X					X					X	
Study Treatment Injection	X					X					X						
Injection Site Grading Scale[12]	X	X				X	X				X	X					
Injection Site Pain VAS[13]	X					X					X						
Injection Site Evaluation[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Behavioural Therapy[15]	X		X	X	X	X		X	X	X	X		X	X	X	X	
EQ-5D-5L											X[16]					X	
SF-36v2											X[16]					X	
MSQ											X[16]					X	
Employment Status and Health Insurance	X[16]					X[16]					X[16]					X	
HCRU	X[16]					X[16]					X[16]					X	

Evaluation	Inj 4	Postinjection 4 Assessments				Inj 5	Postinjection 5 Assessments				Inj 6	Postinjection 6 Assessments				EOS/ET/ Safety Follow-up	
	Wk13 D 85	Wk13 D 86	Wk14 D 92	W15 D 99	Wk16 D 106	Wk17 D 113	Wk17 D 114	Wk18 D 120	Wk19 D 127	Wk20 D 134	Wk21 D 141	Wk21 D 142	Wk22 D 148	W23 D 155	Wk24 D 162	Wk25 D 169[17]	Wk29 D 197[18]
Window	±2	+1	±1	±1	±1	±2	+1	±1	±1	±1	±2	+1	±1	±1	±1	±2	±2
Physical Examination[20]																X	
Review of Treatment Options																X	
EOS																X[20]	

AE = adverse event; BDI-II = Beck Depression Inventory-II; BMI = body mass index; BPI = Brief Pain Inventory; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; COWS = Clinical Opiate Withdrawal Scale; D = Day; ECG = electrocardiogram; eCRF = electronic case report form; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; EOS/ET = End of Study/Early Termination; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; HCRU = healthcare resource utilization; Inj = injection; IXRS = Interactive Voice/Web Response System; MSQ = Medication Satisfaction Questionnaire; PGx = Pharmacogenomic; PK = pharmacokinetic/pharmacokinetics; RNA = ribonucleic acid; SAE = serious adverse event; SC = subcutaneous; SF-36v2 = 36-Item Short Form Health Survey, Version 2; SOWS = subjective opiate withdrawal scale; TLFB = Timeline Followback; UDS = urine drug screen; VAS = Visual Analog Scale; Wk = Week

1. Included blood pressure (BP; supine ≥ 3 minutes), pulse oximetry, pulse rate, respiratory rate and oral temperature. Vital signs on injection days were taken ≤ 60 minutes prior to SC injection and then 0.5, 2 and 4 hours post SC injection (± 15 minutes).
2. A resting 12-lead ECG was taken ≤ 1 hour prior to each PK sample collection.
3. Pulse oximetry was measured from at least 30 minutes prior to SC injection through at least 4 hours postinjection. Results obtained within 30 minutes preinjection and 4 hours postinjection (± 15 minutes) were recorded in the eCRF.
4. Holter monitor recording was obtained from at least 30 minutes preinjection through at least 24 hours postinjection. The Holter monitor must have been applied prior to PK sample collection on injection days to allow an ECG extraction before PK collection.
5. Blood and urine samples were taken ≤ 60 min prior to SC injection.
6. Only for female subjects who were of childbearing potential (not postmenopausal or surgically sterile for at least 1 year).
7. An additional blinded UDS could have been done if use was suspected. Oxycodone may not have shown up in all opiate assays and should have been assessed separately. Prior to the study treatment injection, if the investigator was concerned about subject safety secondary to possible benzodiazepine use, an in-office benzodiazepine urine test may have been performed. If the test was positive, the investigator was to contact the medical monitor or the sponsor to discuss whether or not to administer the study treatment.
8. See PK table (see Appendix 4 of the protocol in Appendix 16.1.1) for exact time points.
9. RNA sample was to be taken on Day 169 or upon ET. See PGx Sampling Schedule (see Appendix 5 of the protocol in Appendix 16.1.1) for exact time points.
10. A PK sample was to be taken as soon as possible after any SAE was reported. If possible, an additional sample should have been collected when the SAE had resolved.
11. Assessments should have been performed prior to study treatment injection and at approximately the same time each day ± 2 hours.

12. Local injection site grading was performed at the time of SC injection (within 10 minutes), 4 hours (± 30 minutes) and 24 hours (± 4 hours) post SC injection.
13. The injection site pain VAS scores were obtained (after the completion of the injection) within 1 minute and at 5, 10, 15, 30, 60 and 120 minutes (± 5 minutes). The timing of the injection site pain VAS should have been measured from the end of the injection.
14. Injection site was evaluated for evidence of attempted removal.
15. Subjects were to receive manual-guided, individual behavioural therapy at least once a week.
16. Assessments should have been performed prior to study treatment injection.
17. For subjects who wished to continue in the long-term safety study of RBP-6000 **OR** subjects who discontinued participation in the study after receiving study treatment, the procedures at Week 25/Day 169 served as the EOS/ET study assessments.
18. Subjects who completed the study but did not meet the eligibility criteria of the long-term safety study of RBP-6000 **OR** subjects who completed the study but did not wish to enrol in the long-term safety study **OR** subjects who discontinued participation after receiving study treatment underwent Week 29/Day 197 EOS assessments.
19. IXRS contacted to confirm study completion or discontinuation status (date and reason for discontinuation).
20. Complete examination (excluding pelvic, breast and rectal), including general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities and a brief neurological assessment.

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/s/

CELIA J WINCHELL
11/30/2017

SHARON H HERTZ
11/30/2017
I fully concur with the analysis and findings of the review team, and with the conclusions conveyed in this memo.