

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209819Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: November 29, 2017

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 209819

Product Name and Strength: Sublocade (buprenorphine extended-release) injection for subcutaneous use, 100 mg and 300 mg

Applicant/Sponsor Name: Indivior, Inc.

Submission Date: November 27, 2017

OSE RCM #: 2017-1067-2

DMEPA Safety Evaluator: Millie Shah, PharmD, BCPS

DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised pre-filled syringe label, pouch labeling, and carton labeling for Sublocade (buprenorphine extended-release) injection for subcutaneous use (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.^{a,b}

2 CONCLUSION

The revised pre-filled syringe label, pouch labeling, and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Shah, M. Label and Labeling Review for Sublocade (NDA 209819). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 12. RCM No.: 2017-1067.

^b Shah, M. Label and Labeling Memo for Sublocade (NDA 209819). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 21. RCM No.: 2017-1067-1.

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/s/

MILLIE C BRAHMBHATT
11/29/2017

OTTO L TOWNSEND
11/29/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 17, 2017

To: Celia Winchell, MD, Clinical Team Leader
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Lisa Basham, MS, Associate Director for Labeling, DAAAP

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Swati Patwardhan, Regulatory Project Manager, DAAAP
Sam Skariah, Team Leader, OPDP
Shenee' Toombs, Regulatory Review Officer, OPDP
Nima Ossareh, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for SUBLOCADE (buprenorphine extended-release) Injection Product Labeling (PI) and Medication Guide (MG).

NDA: 209819
SUBLOCADE (buprenorphine extended-release) injection, for subcutaneous use, CIII

In response to DAAAP's consult request dated June 2, 2017, OPDP has reviewed the proposed prescribing information (PI) and Medication Guide (MG) labeling for the original NDA submission for SUBLOCADE (buprenorphine extended-release) injection, for subcutaneous use.

PI: OPDP has reviewed the proposed draft product labeling received by electronic mail from DAAAP on November 13, 2017, and have provided comments in the attached PI. Specifically, OPDP comments were added on pages 5, 18, 20, 21, 24, and 33.

MG: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI was completed on November 17, 2017, under separate cover.

Thank you for your consult. If you have any questions, please contact Koung Lee at (240) 402-8686 or koung.lee@fda.hhs.gov.

Attachment: Prescribing Information

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/s/

KOUNG U LEE
11/17/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 17, 2017

To: Sharon Hertz, MD
Director
**Division of Anesthesia, Analgesia, Addiction Products
(DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Koung Lee, RPh, MSHS
Regulatory Reviewer Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name), Dosage Form and Route: SUBLOCADE (buprenorphine extended-release) injection, for subcutaneous use, CIII

Application Type/Number: NDA 209819

Applicant: Indivior Inc.

1 INTRODUCTION

On May 30, 2017, Indivior Inc. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 209819 for SUBLOCADE (buprenorphine extended-release) injection. SUBLOCADE (buprenorphine extended-release) injection 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) on June 2, 2017, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SUBLOCADE (buprenorphine extended-release) injection.

2 MATERIAL REVIEWED

- Draft SUBLOCADE (buprenorphine extended-release) injection MG received on May 30, 2017, and received by DMPP and OPDP on November 14, 2017.
- Draft SUBLOCADE (buprenorphine extended-release) injection Prescribing Information (PI) received on May 30, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 14, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
11/17/2017

KOUNG U LEE
11/17/2017

BARBARA A FULLER
11/17/2017

LASHAWN M GRIFFITHS
11/17/2017

Internal Consults

*** Pre-decisional Agency Information ***

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Joan Blair, Health Communications Analyst, DRISK

From: Koung Lee, Regulatory Review Officer, OPDP

CC: Sam Skariah, Team Leader, OPDP
Shenee' Toombs, Regulatory Review Officer, OPDP
Nima Ossareh, Regulatory Review Officer, OPDP
Kate Heinrich Oswell, Health Communications Analyst, DRISK
Carole Broadnax, Regulatory Review Officer, OPDP
CDER-OPDP-RPM
Michael Wade, OPDP

Date: November 16, 2017

Re: NDA 209819
SUBLOCADE® (buprenorphine extended-release) Injection, for Subcutaneous Use, CIII
Comments on draft Risk Evaluation and Mitigation Strategies (REMS) Materials (Submission date: November 14, 2017)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for Sublocade:

- Healthcare Provider (HCP) REMS Materials:

- **Sublocade REMS Program Healthcare Settings and Pharmacy Enrollment Form**
- **Sublocade REMS Program Dear Healthcare Provider Letter**
- **Sublocade REMS Program Fact Sheet**
- **Sublocade REMS Program Website**
- (b) (4)

The version of the draft REMS materials used in this review were sent from Joan Blair of DRISK via email on November 15, 2017. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Sublocade Injection.

General Comment

OPDP recommends that the website, www.SUBLOCADEREMS.com, and toll free number 1-866-258-3905 be directly linked to only Sublocade REMS related information and not be promotional in tone.

We note that a placeholder exists within these documents for the “SUBLOCADE LOGO.” Since the logo has not been included within these documents, OPDP cannot determine if they contain any promotional claims/presentations. Please remind Indivior that REMS materials are not appropriate for use in a promotional manner and should be non-promotional.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Sublocade REMS Program Healthcare Settings and Pharmacy Enrollment Form
- Sublocade REMS Program Dear Healthcare Provider Letter
- Sublocade REMS Program Fact Sheet
- Sublocade REMS Program Website
- (b) (4)

Specific Comments

OPDP considers the following statements promotional in tone and recommends revisions:

- Sublocade REMS Dear Healthcare Provider Letter
- Sublocade REMS Program Website

▪ **Indications/** (b) (4)



We recommend that it be revised to include the complete indication.

- Sublocade REMS Program Dear Healthcare Provider Letter
Sublocade REMS Program Website
Sublocade REMS Program Fact Sheet

▪ **Risks**



- (b) (4)

▪ **Risks**



(b) (4) The Boxed Warning section of the Sublocade PI includes the following risk information (underline emphasis added).

- Serious harm or death could result if administered intravenously.

OPDP recommends including the risk of death in the risk statement in these pieces.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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/s/

KOUNG U LEE
11/16/2017

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research



Date: November 9, 2017

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Dominic Chiapperino, Ph.D., Acting Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Martin Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

From: Alan Trachtenberg, M.D., M.P.H., Medical Officer
Controlled Substance Staff

Subject: **Sublocade** Buprenorphine injectable SC depot, **NDA 209819**
Buprenorphine-Atrigel or RBP-6000
Doses, formulations, routes: 100 & 300 mg in prefilled syringes for
subcutaneous injection
IND 107607
Indication: Opioid Agonist Treatment (OAT) of Opioid Use Disorder (OUD)
Sponsor: Indivior
PDUFA Goal Date: November 30, 2017 (priority review)

Materials

Reviewed: Materials for Study RB-US-13-0002 and abuse related data in NDA 209819, Received May 30, 2017; Responses to Information Requests (IR) for VAS measurement data and analysis; Materials from Sponsor submitted for Advisory Committee (AC) hearing of October 31, 2017.

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I. SUMMARY

1. Background

This memorandum responds to a consult request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) to evaluate the abuse liability assessment and opioid blockade study submitted under 505(b)(2) by Indivior in NDA 209819 and IND 107607, for Sublocade (injectable subcutaneous (SC) depot buprenorphine). DAAAP asked CSS and the statistical team CSS consults, Division of Biometrics VI, to determine whether study RB-US-13-0002 provides evidence that Sublocade provides blockade of the effects of exogenous opioids throughout the one month dosing period. Meeting minutes and correspondence between the Sponsor and DAAAP have emphasized that FDA believes full opioid blockade, and not merely an attenuation of opioid effect, to be an important product attribute when patients who receive RBP-6000 are exposed to opioid doses typically used by persons with an active opioid use disorder (OUD). This product is offered in prefilled syringes with doses of either 100 mg or 300 mg of buprenorphine (BUP), carried in the proprietary “Atrigel” delivery system, intended to provide a long-acting SC depot of BUP for systemic release of a stable level over (at least) the following month. The drug product is indicated for once monthly treatment of moderate to severe OUD in patients who have already undergone induction with a transmucosal BUP containing product to suppress signs and symptoms of opioid withdrawal. The Sponsor is recommending that RBP-6000 be used as part of a complete treatment plan to include counselling and psychosocial support, as

with previous BUP products for MAT. The recommended dose is initially a SC injection of 300 mg, to reach a therapeutic level with that first dose, followed by subsequent monthly injection of either 100 mg or 300 mg each month, based on clinical response.

Buprenorphine is a partial mu-agonist opioid and is the only C-III opioid (with or without naloxone in combination) approved for the treatment of OUD. Therefore, it is the only opioid medication covered by the Drug Addiction Treatment Act of 2000 (DATA-2000). DATA-2000 established a legal pathway for Office-Based Opioid Treatment (OBOT) to be offered by physicians outside of the special clinics designated and licensed by DEA as “Narcotic Treatment Programs” (NTPs, or “Methadone clinics”). Buprenorphine can also be used in these specially designated clinics. It was first approved as a new molecular entity (NME), indicated for pain treatment, in 1981 and marketed as Buprenex injectable under NDA 018401. It was approved as a sublingual tablet for the treatment of OUD in 2002 under NDA 020732 for Subutex (BUP hydrochloride) sublingual tablet, and another sublingual tablet in combination with naloxone, Suboxone.

Opioid agonists or partial agonists such as BUP have several properties that may contribute to their effectiveness in the treatment of opioid addiction. They alleviate the acute symptoms of opioid withdrawal and drug craving. They also attenuate or block the acute effects of exogenous opioids when the patient may have a “lapse” to drug use and help prevent immediate repetition of the lapse and extension into a full relapse of uncontrolled self-administration of drugs. Opioid agonists such as BUP can also be diverted and abused by patients and others. While not posing as high a mortality risk of overdose as from full agonists such as methadone, BUP is itself a drug of abuse such that safeguards against abuse and diversion are required.

The first BUP product to provide long term treatment without need for dispensing or self-administration was a subcutaneously implanted BUP rod, marketed as Probuphine, approved under NDA 204442 on May 26, 2016. Five of these rods can be surgically implanted to provide 6 months of continuous BUP. However, a minor surgical procedure is required for administration and another for removal at the end of their use. Approval was for only one additional implantation after the first. Such parenteral administration by health professionals offered advantages over the self-administration of sublingual BUP by potentially increasing treatment compliance and minimizing abuse and diversion of BUP. Sublocade is intended to offer similar benefits, but without a need for surgery. Although Sublocade will require monthly visits, rather than every 6 months, the decreased procedural risk, and increased access that could be offered by the growing pool of DATA-waived health professionals are two potential advantages of the formulation to consider.

Buprenorphine is a controlled substance, listed in Schedule III of the Controlled Substance Act (CSA). The Sponsor does not propose any change in schedule for their product.

2. Conclusions

1. Sublocade (RBP-6000) is a first-in-class SC long-acting depot formulation of BUP for Buprenorphine Injection Medication Assisted Treatment (BI-MAT) in the treatment of OUD after initial induction and stabilization with short-acting BUP products.

2. This NDA is a 505(b)(2) submission using Subutex (NDA 20732) as the Reference Listed Product. Buprenorphine is a well characterized partial mu-opioid receptor agonist and kappa-opioid receptor antagonist, and is in currently marketed products for the treatment of OUD and pain.
3. Buprenorphine is a Schedule III opioid (“Narcotic”). The Sponsor is not requesting any change in this classification of their product.
4. As an opioid approved by FDA for the treatment of OUD, Sublocade’s medical use will be regulated under the Drug Addiction Treatment Act of 2000 (DATA-2000). Prescribers must document their adequate training to the Substance Abuse and Mental Health Services Administration (SAMHSA) and receive a waiver from the DEA.
5. The large amount of BUP (100-300 mg) in each device (intended to congeal after injection), and the easily injectable nature of the drug/device product, creates a significant risk for intravascular self-injection by persons with OUD, potentially leading to severe life threatening complications. Therefore, administrative and regulatory controls will be required to keep the product completely under the control of health professionals, until administration of the drug by such professionals, while the remainder of the product is properly disposed.
6. This new type of product would provide a BUP treatment option that requires monthly, rather than daily (or once every 2-3 days), administration. This new BI-MAT product may lead to a variety of new possibilities for creating greater access to MAT for more patients with OUD, while decreasing any collateral diversion and abuse that might otherwise have complicated this greater access.
7. RBP-6000, 300 mg, provides significant attenuation of the reinforcing subjective effects of 6 to 18 mg of IM hydromorphone (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. Pending statistical input, final labeling regarding this blockade study is now being negotiated with the Sponsor.
8. Overall, if the Sponsor’s REMS meets the requirements of the CSA, DATA-2000, and the standards of training and practice promulgated by SAMHSA, the benefits of this BI-MAT should outweigh the risks of misuse, abuse, diversion and overdose.

3. Recommendations

1. From the CSS perspective, this product may be approved. The Sponsor’s proposal for maintaining this buprenorphine product in Schedule III under the CSA is acceptable.

2. Sponsor should provide detailed narratives on misuse, abuse, addiction, diversion and overdose in their submission of post approval periodic safety reports. In particular, they should identify any new methods of obtaining, diverting or tampering of this formulation, or otherwise having the product escape the administration safeguards put in to place under DATA-2000 and the product's REMS.

II. DISCUSSION

1. Chemistry

1.1 Substance Information

The active pharmaceutical ingredient (API) in RBP-6000 is BUP base. Chemical name: (2S)-2-[17-(Cyclopropylmethyl)-4,5 α -epoxy-3-hydroxy-6-methoxy-6 α ,14-ethano-14 α -morphinan-7 α -yl]-3,3-dimethylbutan-2-ol; or 21-Cyclopropyl-7 α -[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endoethano-6,7,8,14-tetrahydrooripavine; or 6,14-Ethenomorphinan-7-methanol,17-cyclopropylmethyl- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-, [5 α ,7 α (S)].

Buprenorphine base is a white to off-white crystalline powder, free from any visible particulate contamination. Buprenorphine is very slightly soluble in water, freely soluble in acetone, soluble in methanol, slightly soluble in cyclohexane and highly soluble in N-methyl-2-pyrrolidone (NMP)¹. It dissolves in dilute solutions of acids. CAS registry number: 52485-79-7. Empirical Formula: C₂₉H₄₁NO₄

1.2 Product Information

RBP-6000 is a sterile parenteral drug product consisting of a 200 mg/mL solution of BUP base in the proprietary ATRIGEL® delivery system. This system consists of a biodegradable polymer, 50:50 poly (lactide-co-glycolide) with a carboxylic acid end group (PLGH), dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). The formulation is (b) (4) a syringe, which comes as an integral part of the drug/device product. The syringe is packaged with an oxygen absorber in a foil laminate pouch. A needle is provided to inject the product subcutaneously.

The product contains 200 mg of BUP per mL and consists of 18% BUP by weight. The formulation's density is approximately (b) (4) g/mL.

The components of the product are listed in the Sponsor's Table 1:

Table 1

Components for RBP-6000

¹ Solubility Definitions; "very soluble" indicates that less than 1 mL of solvent is needed to dissolve 1 g of solute; "soluble" indicates that approximately 10- 30 mL of solvent are needed to dissolve 1 g of solute; "slightly soluble" indicates that 100 mL to 1,000 mL (1 l) are needed to dissolve 1 g of solute; and "very slightly soluble" indicates that volumes as high of 1- 10 liters of solvent are required to dissolve 1 g of solute. Sokoloski, T.D. (1995). Solutions and Phase Equilibria. Remington: The Science and Practice of Pharmacy A. G. Gennaro. Easton, Pennsylvania, Mack Publishing Company. **Volume I:** 195.

Component	Weight Percentage in Formulation (%)	Function
Buprenorphine Base	18	Active Pharmaceutical Ingredient
N-methyl-2-pyrrolidone	(b) (4)	Solvent
50:50 Poly(DL-lactide-co- glycolide)	(b) (4)	Polymer

The Atrigel Delivery System functions to form a depot upon SC injection. It releases BUP over the course of multiple months

2. Nonclinical Pharmacology

The Sponsor did not perform any new animal studies to examine abuse-related characteristics or other basic pharmacologic parameters of BUP. The Sponsor's new non-clinical studies were all conducted in support of the specific formulation and assessment of the RBP-6000 product.

Buprenorphine has high affinity for mu and kappa opioid receptors with lower affinity for delta receptors. In vitro studies have shown low mu agonist activity, very low delta activity and undetectable kappa agonist activity. It is generally classified as a mu-opioid partial agonist with mixed agonist and antagonist effects. This leads to a lower abuse and physical dependence profile than typical full agonists such as morphine and lower respiratory depressant effects when compared to mu-opioid full agonists.

The in vivo opioid effects of BUP are consistent with its biochemical and in vitro activity. It acts as a mu-opioid partial agonist in antinociceptive assays and as a kappa antagonist. Compared to other opioids, BUP has a very high receptor affinity. It produces a gradual inhibition of guinea pig ileum contraction which is resistant to reversal by naloxone. Buprenorphine's offset time from opioid receptors, once bound in isolated tissue, is too long to measure, and in receptor binding assays can be 15 times slower than that for naloxone. This is consistent with a continued pharmacodynamic (PD) activity that continues somewhat longer than might be expected based only on pharmacokinetic (PK) measures and the observation that BUP's agonist effects can be prevented by prior presence of opioid antagonists, but not reversed by antagonist administered afterwards (Cowan 1977, Kajiwara 1986). Buprenorphine binds very tightly to the opioid receptor and this very strong association for the receptor leads to a long duration of clinical effect.

3. Clinical Pharmacology

The PK of RBP-6000 was examined in subjects with OUD by administration of single SC injections of 50 to 200 mg of BUP, without any sublingual (SL) pretreatment. The initial release of BUP leads to a maximum plasma concentration after about 24 hours. This peak is then followed by a declining concentration to a relatively stable level for the next 4 weeks, as would be expected from the steady release of BUP from the ATRIGEL formulation. In some subjects a second peak in plasma concentration is also observed between 6 and 11 days after a first injection. The terminal plasma half-life of BUP from RBP-6000 is reported to be from 1,037 to 1,429 hours (43 to 60 days). Increase in BUP plasma concentration is less than proportional to increases in the initial dose of RBP-6000. An increase in dose by a factor of 4, from 50 to 200 mg, leads to a 2.4-fold increase in C_{max} and a 3.4-fold increase in area under the curve (AUC_{0-inf.}) Pre-treatment with SL BUP, as directed in the Sponsor's

label and as provided in the clinical trials reported in this application, may slightly increase the subsequent plasma concentration after the initial SC injection of RBP-6000. The sponsor estimates that a steady state plasma level of BUP is reached within 6 monthly doses of RBP-6000. Elimination of BUP occurs primarily through hepatic metabolism, principally to norbuprenorphine, by cytochrome P450; CYP 3A4 and CYP2C8. Norbuprenorphine is subject to glucuronidation. Norbuprenorphine does have some lesser pharmacologic opioid activity, but its plasma concentrations after RBP-6000 injection are reported to be 0.2 to 0.4 those of BUP and norbuprenorphine has only limited penetration of the blood-brain barrier.

3.1 Drug/Product Interactions

When administered to a patient who has a physical dependence on opioid agonists (not already in withdrawal), BUP, as a partial agonist with high affinity for the mu receptor, will displace full agonists from the mu receptor and may precipitate an opioid withdrawal, much the same as administration of a full antagonist. When administered to a patient already in withdrawal, the buprenorphine will occupy available receptors and thereby alleviate withdrawal. For this reason, induction with buprenorphine for medication assisted therapy (MAT) of OUD requires an assessment of current physical dependence and withdrawal prior to the first dose of BUP.

Benzodiazepines, other sedatives, and other CNS depressants such as alcohol may enhance or add to the potential depressant effects of BUP. As a partial agonist with a ceiling effect, BUP is unlikely on its own to cause loss of consciousness or life-threatening hypoventilation, it can contribute to these when combined with other CNS depressants, potentially leading to apnea and death.

4. Clinical Studies

4.1 Opioid Blockade Study in Human Subjects with Opioid Use Disorder

4.1.1 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 of BUP (RBP-6000). Buprenorphine plasma levels and the safety of SC injections were also examined. 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.”

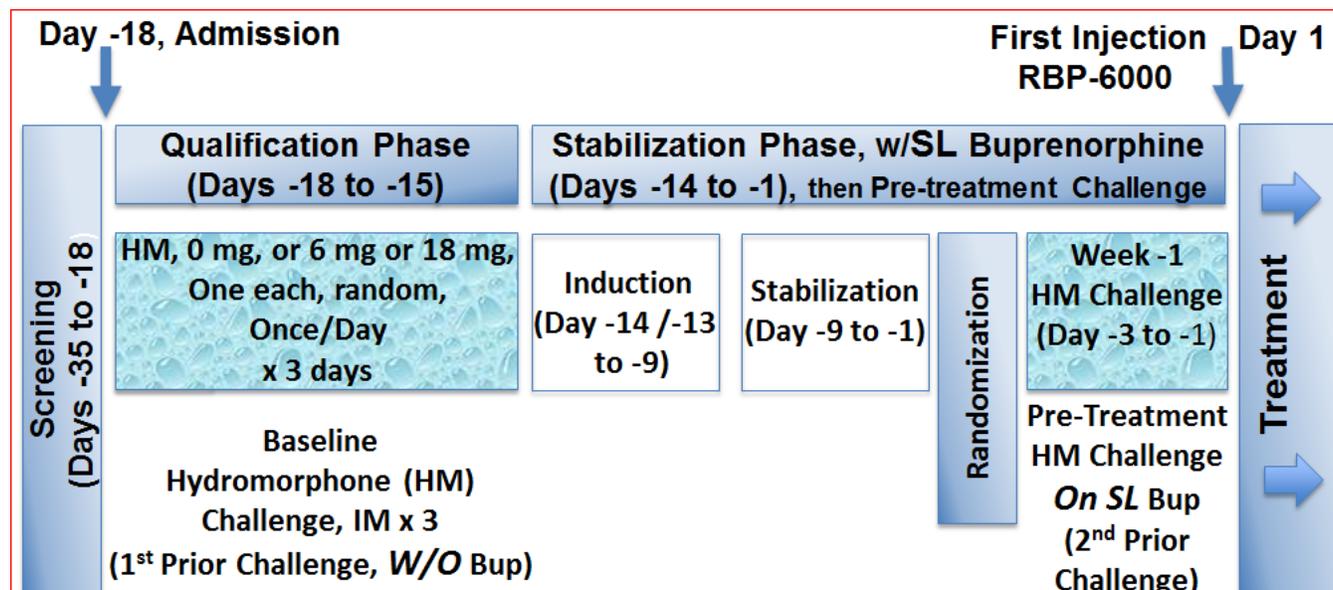
The reinforcing effects of each challenge day's randomized IM morning challenge, in each 3-day set of changing doses (0mg/day or 6mg/day or 18mg/day HM IM), were evaluated in a choice task (relative to money). Subjects were asked to perform, later each day, of the weekly 3-day challenge sets, at least 5 hours after each day's challenge injection. On each challenge day the 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, if they valued that more than the anticipated 1/12 of whatever reward they had felt from that morning's dose. For each day's 12 choice trials, a subject chose between earning 1/12 of the total challenge dose they had received that morning, to be added together into another dose (to a cumulative maximum equaling that of the morning dose) to receive at the end of the day. Alternatively, they could get \$2.00/trial for each of that day's 12 trials, to a maximum total of \$2.00 x 12 trials=\$24.00/challenge day. To earn each of that day's 12 alternative choices of the 1/12 portions of that morning's dose or \$2.00 cash, the subjects had to perform a specified and predictably increasing number of repetitive mouse clicks, each click favoring a choice of money or drug by clicking on that choice. The number of clicks to earn the drug or money for each 12th of their eventual rewards for that day increased across each of that day's 12 trials. For each trial's choice of that 12th of the day's total cash and drug reward, the number of clicks required rose from 5 to 40, to 70, to 120, to 180, to 260, to 395, to 555, to 775, to 1110, to 1558, to 2160 clicks/trial, in 12 exponential increments (across that day's 12 trials), creating a progressive ratio schedule of reinforcement. The number of clicks to earn each 12th of the day's reward for that series of clicks/ task to choose, by clicking on cash (for 1/12 of the \$24.00) or drug (1/12th of that morning's drug dose [0mg, 0.5 mg, or 1.5 mg]) rose independently of each other until all of that day's 12 portions were chosen for the favorite of the two (generally starting with drug, if the subject had felt drug liking that morning) or, until the subject's "breakpoint" was reached to switch work for their 2nd choice (generally cash), starting again at 5 clicks, increasing exponentially again until all 12 trials were completed for the day, with all 12 fractional choices earned (or until the subject gave up clicking for that day). The highest number of clicks "worked" to earn each 12th of that morning's challenge dose for repeat at the end of the day was counted as that trial's breakpoint, with breakpoints recorded for each of the 3 dosed days. For instance, if the subject had felt some drug liking that morning and wanted to repeat that entire dose in the evening, they would have worked 5 clicks for the first 1/12th, providing a growing number of clicks on "drug" for each succeeding series of the 12, until the last 12th required all 2160 clicks on drug. However, if the subject decided to forgo the final 12th of the day's dose and be satisfied with 11/12 of the morning dose, he could opt to click just 5 more times on cash, to earn \$2.00 instead, and that would be his breakpoint for that series.

The continuing safety of RBP-6000 was also evaluated, as a depot injection of 300 mg, in these OUD subjects who had been inducted and stabilized on sublingual (SL) BUP (Suboxone [buprenorphine/naloxone] sublingual film) with doses of 8-24 mg/day. Stabilization was followed by randomized assignment of subjects to groups that would each receive a specified 12 week sequence of 12 weekly sets of 3 days in a row of HM challenges, with the assigned sequence's changing (but initially randomized for each groups' sequence) 3 dose sets of 0mg, 6mg or 18 mg of IM HM. One final baseline 3 day HM challenge set, while on SL BUP (days -4 to -1, referred to as "week 0") was followed by the treatment period (for all sequence groups) of 2 RBP-6000 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 order of each set in each group's 12-set sequence was initially

randomized, but the 3-day sets were then grouped into 12-set sequences, one sequence of 12 three day sets (over 12 weeks) for all subjects randomly assigned to that group. Randomization was just prior to the baseline set of challenge doses (days -4 to -1) prior to injection #1 on Treatment Day 1 (Figure 1).

Figure 1:

Study RB-US-13-0002 Schematic

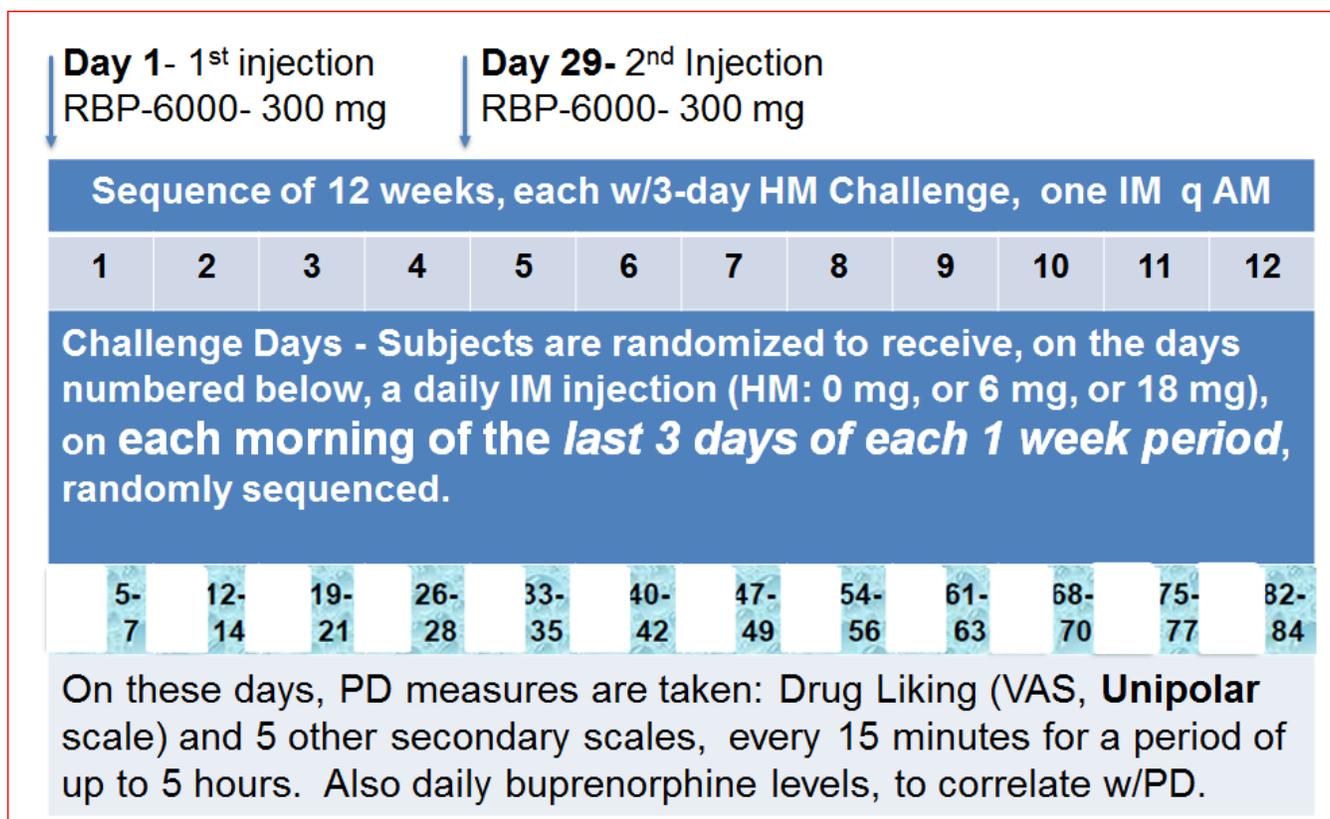


The study consisted of a Screening Phase, a Qualification Phase (Baseline HM Challenge Phase), an Induction-Stabilization and Opioid Blockade Testing Phase, and a Treatment Phase (Figure 2). Eligible subjects were admitted to the clinical facility and established their final qualification by responding appropriately to IM HM and differentiating it from placebo (detailed below). Qualified subjects entered into the Induction-Stabilization Phase of the study where they received 8 to 24 mg SL buprenorphine. Once stabilized on the SL BUP dose, subjects were randomized to receive either 6 mg or 18 mg of IM HM, or placebo, daily in random order and double-blind manner, for the last 3 consecutive days of each week for the 12 weeks.

The treatment period (Figure 2) was then initiated with each subject's first injection of 300 mg of RBP-6000 on treatment day 1. Starting on day 5 each subject then received a daily injection of either placebo (HM 0 mg) or an injection of 6mg or 18mg of HM in a double-blind fashion and in random order during a 3-consecutive day set for four weeks starting 5 days after receiving the first treatment dose (days 5, 12, 19 and 26). At week 5, subjects received a second 300 mg RBP-6000 injection SC on day 29, and five days later the subjects continued receiving the 3 day sets of daily IM HM challenge doses (placebo, HM 6 mg and 18 mg) in their 12 week randomly assigned group sequence (of 12 sets of 3 consecutive days each week) for the final 8 weeks of the 12.

Figure 2

Study RB-US-13-0002 Treatment Phase



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.

The study enrolled 39 subjects with moderate to severe OUD to reach a goal of at least 24 completers of all the HM challenges during study Weeks 1-4. Subjects were admitted to the clinical facility for 3 consecutive days, starting the night before the first challenge day, for each of the 12 weeks of the study following the first RBP-6000 injection (see Population Section). From day -35 to day -19, subjects were screened and then admitted to the clinical facility on day -18 for a qualification and baseline HM challenge (3 daily doses in random sequence), day -18 to day -16. Subjects with a qualifying response (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 were then entered in to the full trial. 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. Subjects had another HM challenge set on days -3 through -1. On day 1, subjects who still met all criteria discontinued SL BUP and received their first injection of RBP-6000. Subsequently, subjects were released from the clinical facility on day 2. 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 RBP-6000 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.

4.1.2 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 2.

Table 2

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
	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/m ²)	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		

4.1.3 Statistical Methodologies of the Blockade Study

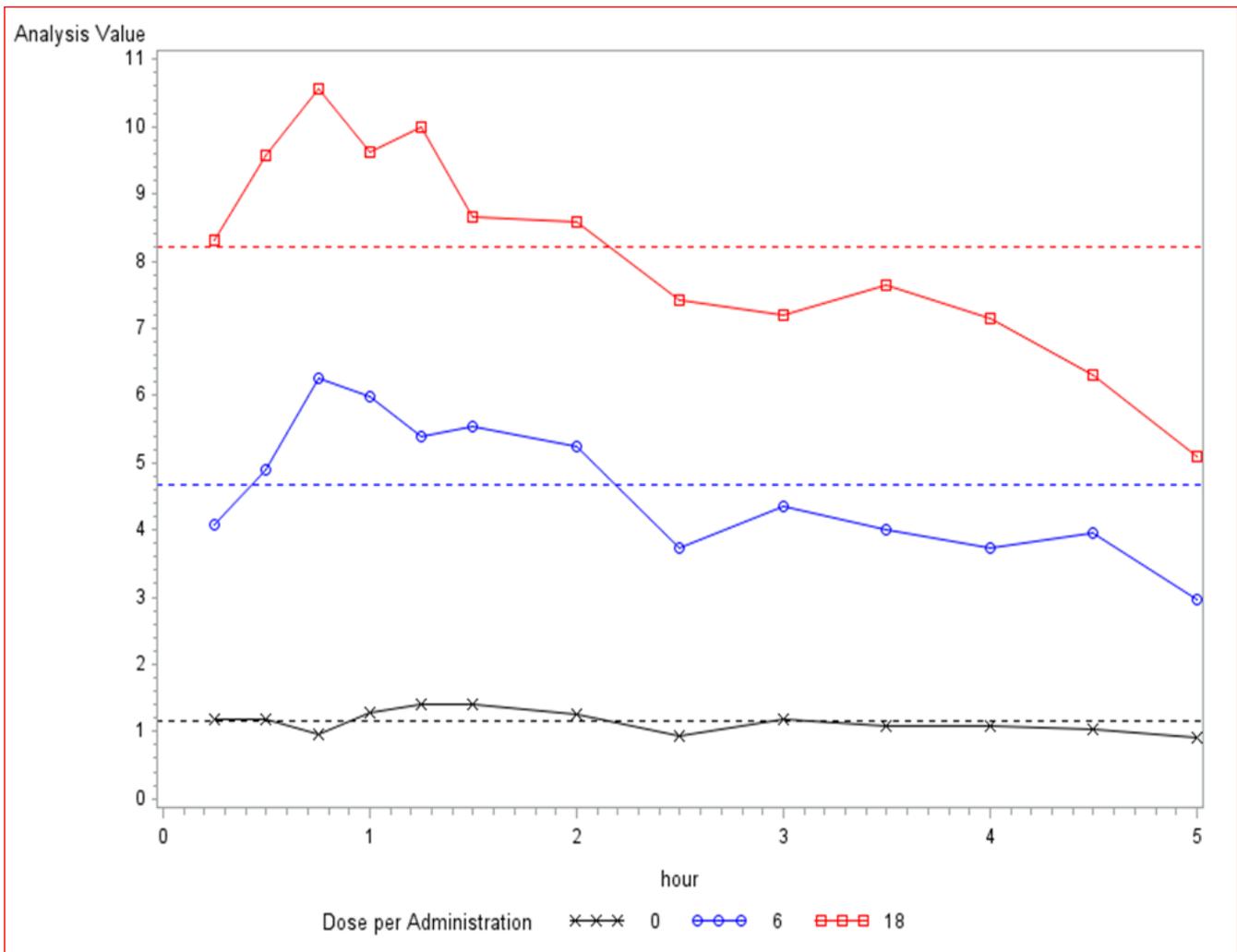
The opioid blockade study was submitted by the Sponsor to be supportive of their pivotal study, RB-US-13-0001. The endpoint used for analysis of the blockade study was the mean score of “Drug Liking” VAS. Secondary endpoints included “Any Drug Effect,” “Good Drug Effect,” “Bad Drug Effect,” “Sedation,” and “High”. The primary analysis is the (modified) intention-to-treat (mITT) analysis.

There were a total of 39 subjects randomized into the Treatment Phase study with 38 subjects included in the ITT population. The subject who was not included in the ITT population, but was in the safety population, did not complete the study and was lost to follow-up. There were 29 completers at the end of Week 4 (78.9%), with 2 lost to follow-up, three due to physician decision, and three withdrawals by subject choice.

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 Emean. This was then used for comparisons between the drug liking effects of placebo and HM. This might have potentially biased toward a finding of no difference between 0mg and 18 mg of HM, and could have lead toward an appearance of more blockade (and therefore greater significance) for that finding, than could have been shown measuring the differences between the peaks at Tmax, which are considered more clinically relevant. This is illustrated in Figure 3, provided by the statistical team.

Figure 3

Drug Liking VAS measured every 15 minutes for 5 hours post-HM, Week 1



While the peak effects, or Emax, are visibly distinct and different around the Tmax, expected about an hour after IM injection, these differences might be obscured if the Emeans were compared, rather than those Emax values. Use of the Emax is recommended in the *2017 FDA Guidance for Industry Assessment of Abuse Potential of Drugs*² because it appears to have the greatest clinical relevance and salience to opioid abusers.

Another problem with the Sponsor’s analysis was that they applied a non-inferiority (NI) margin of 11 to the VAS measures from their Unipolar Scale of Drug Liking. If the VAS from IM HM exceeds the VAS from placebo by more than the non-inferiority margin, then the HM is more than just marginally more reinforcing than placebo. Unfortunately, this NI margin of 11 had been derived and standardized for data from Bipolar Scales.

² <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

This may have been too stringent a test. When the more sensitive Emax data (as recommended in the Guidance), was applied to the overly-stringent NI margin of 11, the Emax difference exceeded that blockade and no longer looked significant. Consequently, a more appropriate NI margin was determined, as detailed in Dr. Wei Liu's Statistical Review and Evaluation. Final labeling (Section 14) detailing the Opioid Blockade Study will incorporate the opinions expressed in this statistical review.

4.1.4 Results and Conclusions of the Opioid Blockade Study

RBP-6000, 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.

4.2 Other Clinical Studies in the RBP-6000 Development Program

The clinical development program for RBP-6000 consisted of the following studies. All studies enrolled subjects with a diagnosis of opioid dependence (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision [DSM-V-TR]), or moderate or severe OUD (DSM-5). The Phase 3 studies included manual-guided individual drug counselling (IDC) as part of the treatment program.

-Study RB-US-10-0011 - a Phase 1 open label (OL) single-dose first time in human (FTIH) safety and tolerability study.

-Study RB-US-11-0020 - a Phase 1 OL single-ascending-dose (SAD) safety and tolerability study.

-Study RB-US-13-0006 - a Phase 1 OL single-dose molecular weight (MW) study to assess the relative bioavailability of RBP-6000 formulated with 2 different MWs of 50:50 poly-D, L lactide-co-glycolide with an acid end group (PLGH) polymer in comparison to intermediate MW of PLGH polymer.

-Study RB-US-12-0005 - a Phase 2 OL multiple ascending dose (MAD) safety and tolerability study including a positron-emission tomography (PET) imaging sub-study.

-Study RB-US-13-0001 - a Phase 3 double-blind (DB), placebo-controlled efficacy, safety and tolerability study.

-Study RB-US-13-0003 – an ongoing Phase 3 long-term OL safety and tolerability study.

Along-term treatment extension study (IND-6000-301, an extension of Study RB-US-13-0003) was initiated after the data cut-off date. Because the average waitlist time for an OUD patient to get into a treatment clinic/facility is 6 months, the Sponsor included this “compassionate use” trial to provide up to 6 additional months of treatment for subjects who completed Study RB-US-13-0003, allowing sufficient time for them to secure subsequent OUD care. Data from this study are not included in the Sponsor's submission.

4.3 Safety Profile and Adverse Events

Safety topics of special interest were selected by the Sponsor based on the pharmacology of BUP. These included hepatic disorders, opioid withdrawal signs and symptoms, central nervous system (CNS) depression, respiratory depression and orthostatic hypotension. Hepatic disorders were also addressed using the clinical chemistry laboratory data. In addition, monitoring of pancreatic functioning was included in several clinical studies due to a nonclinical safety finding of pancreatic acinar cell apoptosis which was subsequently believed to be secondary to stress. No clinical differences were observed based on evaluation of treatment emergent adverse event (TEAE) profiles for subjects who received the Suboxone film taper vs. did not receive the Suboxone film taper (did not receive Suboxone following initiation of RBP-6000 or placebo) at the beginning of the double-blind treatment phase in the phase 3 study.

The TEAE profile across all studies was consistent with the known safety profile for BUP. They were reported in a higher percentage of subjects in the 300 mg/100mg and 300 mg/300 mg groups compared with the placebo group, respectively, as follows: 76.4% and 66.7% vs. 56.0%. No individual TEAEs were reported in > 10% of subjects in the active total 300 mg/100 mg or 300 mg/300 mg groups. The most common TEAEs ($\geq 5\%$ of subjects) reported in the active total group were headache, constipation, nausea, injection site pruritus, vomiting, insomnia and upper respiratory tract infection. The percentage of subjects with the most common TEAEs was generally similar across treatment groups, although constipation was reported in only the active treatment groups and upper respiratory tract infection was reported more frequently in the active treatment groups compared with the placebo group.

There was 1 fatal SAE report (gunshot wound) in the RBP-6000 clinical development program. The death was declared a homicide by police and was considered unrelated to study treatment. Other SAEs were rare (maximum of one subject) and generally occurred at a similar frequency in the active drug and placebo groups.

There were 2 reports of surgical removal of the RBP-6000 depot. One subject in the opioid blockade study (RB-US-13-0002) had the depot removed (study day 13) after withdrawing consent and requesting removal. Another subject in a Phase 1 study (RB-US-13-0006) had the RBP-6000 depot removed (study day 16) due to a serious adverse event (SAE) of abnormal liver chemistry values. The subject subsequently tested positive for hepatitis C within 1 month. No complications were reported following the RBP-6000 depot removal for either subject. No RBP-6000 depots were surgically removed in the Phase 3 studies. There were no reports of attempted depot removal by subjects themselves.

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

There were 3 reported overdoses from non-study drugs, one each of heroin, diazepam, and trazodone. There was no evidence of abuse or drug accountability issues in the clinical trials conducted by the Sponsor. There were no reported attempts, by subjects, to remove the depot from the skin, and no reports of diversion or problems with drug accountability.

5. Regulatory Issues and Assessment

The epidemic of OUD and overdose deaths continues to challenge the overall public health and demands both better utilization of existing treatments and development of new treatments more effective, or as effective and more accessible, than those existing. For many individuals with OUD the most effective treatments are MAT, often assisted by opioid medications with at least partial agonist effect at the mu receptor. Ironically, as these opioid agonist treatment (OAT) medications become more prevalent, they themselves may increase the risk of abuse and addiction. While diverted BUP carries a lower risk of overdose death than full agonists such as methadone, concern remains for BUP's diversion potential to create its own increased risk of contributing to new OUD, as a potential "gateway" opioid.

DATA 2000 increased access for patients to MAT by allowing a prescription to be issued for an opioid (in Schedules III, IV or V) as an FDA-approved treatment of OUD. Dispensing, even at the initiation of OAT, became legal under Federal and State law for the first time since the Narcotic Addict Treatment Act (NATA) was enacted in 1974. It allowed practitioners with DATA waivers from DEA (with authorization from the SAMHSA Center for Substance Abuse Treatment (CSAT)) to dispense (including administration) or prescribe Schedule III, IV or V controlled substances specifically approved by the FDA for "narcotic addiction" (treatment of OUD). The FDA subsequently approved the first two schedule III products indicated for office-based opioid treatment (OBOT) under DATA on October 8, 2002, with SL BUP as Subutex and Suboxone (combined with naloxone in ^(b)₍₄₎ of the amount of BUP).

These medications were typically dispensed in monthly (or weekly, at first) amounts, requiring weekly or monthly contact with health care providers. Much of each patient's medication supply then passed out of the control of health care providers and became potentially available for diversion. Injectable BUP products, requiring only monthly provider contact, but without any medication leaving in the hands of the patient, provide for the possibility of greatly expanding the treatment population and expanding access to treatment, but without any collateral increase in the amount of drug accessible for diversion.

The only other form of BUP available as a long-term SC depot supply is Probuphine. It requires surgical implantation and removal for both the initial administration and for the medically necessary removal of the implants after exhaustion of its 6 month supply of BUP. Alternatively, a SC injection is a procedure that can be done, without any additional training, by most health professionals and does not require removal.

Since intentional intravascular injection always remains a concern in the treatment of OUD patients, many of whom have considerable experience with the self-administration of IV drugs, it is important that this product stay out of the hands of patients with OUD. The product's REMS should include measures to minimize this hazard by preventing any possible opportunity for patients to possess the product in any fashion other than by the "internal possession" of the SC depot after safe injection by a health professional.

This product may be associated with a risk of improper self-administration by drug-injectors who might experiment with an intravascular route. This could potentially form a thrombus capable of limb-threatening occlusion of the vein (or artery) or an embolus, potentially travelling to the heart and lungs. The Sponsor's proposed REMS includes elements to assure safe use (ETASU) with additional healthcare setting certification to 1) mitigate the risks of accidental overdose, misuse and abuse, 2) inform prescribers, pharmacists, and patients of the serious risks of the product, and 3) inform prescribers, pharmacists and patients about the long acting nature of RBP-6000. These ETASU are

ultimately enforceable by FDA, and therefore by the Sponsor and all subsequent legitimate purchasers, through legally enforceable contracts and scope of practice or other relevant regulations (as determined by State Health Professions Practice Acts), as well as DATA-2000 and the CSA. These provide for as much enforceable legal control as possible, through the point of administration to the ultimate end-user.

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/s/

MARTIN S RUSINOWITZ
11/09/2017

SILVIA N CALDERON
11/09/2017

DOMINIC CHIAPPERINO
11/10/2017

**Interdisciplinary Review Team for QT Studies Consultation:
QT Study Review**

IND or NDA	NDA 209819
Brand Name	RBP-6000
Generic Name	Buprenorphine injectable
Sponsor	Indivior Inc.
Indication	Treatment of moderate to severe opioid use disorder in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine containing product.
Dosage Form	Subcutaneously (SC) injection
Drug Class	Partial mu-receptor agonist
Therapeutic Dosing Regimen	<ul style="list-style-type: none"> - The recommended dose is 300 mg monthly - The dose may be decreased to 100 mg based on tolerability
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	<ul style="list-style-type: none"> - Single dose: 300 mg SC injection - Multiple dose: 300 mg SC once monthly injection
Submission Number and Date	001, 5/30/2017
Review Division	DAAAP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

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. We cannot accept the sponsor's analysis of the pooled data where differences in the study conditions can cause bias in results (see section 1.2).

The ECG data collected in the pivotal efficacy study (RB-US-13-0001), however, 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 (DARRTs [05/27/2010](#)). The following observations support excluding large mean increases in the QTc interval:

- No large increase in the mean (upper 95% CI) Δ QTcF 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 Δ QTcF 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 \geq 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.

1.2 REVIEWER'S COMMENTS

The reviewer has the following concerns with the provided concentration-QTc analysis from the sponsor:

- The ECG acquisition and ECG measurement at baseline and during the treatment phase are different across studies.
- The study control procedures (e.g., placebo control, patient handling) are different across studies.
- There is 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.

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT:

12.2 Pharmacodynamics

Cardiac Electrophysiology

Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of TRADENAME on the QT interval in five clinical studies including the Phase 3 study. In a Phase 3 study, seven subjects had an increase from baseline QTc greater than 60 msec at any time [2/203 subjects (1.0%) in the 300 mg/100 mg group and 5/201 subjects (2.0%) in the 300 mg/300 mg group] and one (b) (4) in the 300 mg/300 mg group was found to have a QTc greater than 500 msec. These QTc findings were all sporadic and transient and none led to aberrant ventricular rhythm. Review of ECG and adverse event data provided no evidence for (b) (4) syncope, seizure, or ventricular tachycardia or fibrillation.

(b) (4)

QT-IRT's following proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

5.x

(b) (4)

TRADENAME has been observed to prolong the QTc interval in some patients participating in clinical trials. Consider these observations in clinical decisions when prescribing TRADENAME to patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Periodic electrocardiographic (ECG) monitoring is recommended in these patients. Avoid the use of TRADENAME in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval. [See *Clinical Pharmacology* (12.2)]

12.2 Pharmacodynamics

Cardiac Electrophysiology

Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of TRADENAME on the QT interval in five clinical studies including the Phase 3 study. In a Phase 3 study, seven patients had an increase from baseline QTc greater than 60 msec at any time [2/203 patients (1.0%) in the 300 mg/100 mg group and 5/201 patients (2.0%) in 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. These QTc findings were all sporadic and transient and none led to aberrant ventricular rhythm. Review of ECG and adverse event data provided no evidence for syncope, seizure, or ventricular tachycardia or fibrillation.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Buprenorphine is a partial mu-opioid receptor agonist. It is currently indicated for the treatment of opioid use disorder or opioid dependence and for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

QTc prolongation has been observed in healthy volunteer studies for other buprenorphine products.

3.2 MARKET APPROVAL STATUS

The list of buprenorphine products that are currently approved and still being marketed for the treatment of opioid use disorder or opioid dependence (highlighted in grey rows) and for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (highlighted in orange rows) are shown in Table 1 below:

Table 1: List of approved and currently marketed buprenorphine products

Generic/Chemical Name	Trade Name	Sponsor	Dosage form(s)
Buprenorphine	Subutex (generics only)	Indivior	Sublingual tablet
Buprenorphine (modified release product)	Probuphine	Braeburn (Previously Titan)	Implant
Buprenorphine/Naloxone	Suboxone tablet (generics only)	Indivior	Sublingual tablet
	Suboxone film (also generics)	Indivior	Sublingual film
	Bunavail (also generics)	Biodelivery Science International	Buccal film
	Zubsolv (also generics)	Orexo AB	Sublingual film
Buprenorphine	Belbuca	Biodelivery Science International	Buccal film
Buprenorphine (modified release product)	Butrans®	Purdue Pharma	Transdermal system

Note: Rows with grey background are buprenorphine products approved for the treatment of opioid use disorder or opioid dependence; while the rest are approved for

management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Source: Adapted based on the FDA AC Backgrounder Package for NDA 209819, Table 1, Page 15

3.3 PRECLINICAL INFORMATION

As stated in the 2002 publication by Katchman AN et al,²⁴ buprenorphine may represent a safer alternative (with respect to I_{HERG}) to methadone or LAAM for the treatment of narcotic addiction. Based on the results of multiple in vitro studies, the authors concluded that the effects on I_{HERG} channel is considerably stronger for methadone than for buprenorphine at the concentrations achieved after therapeutic use of the drugs.²⁹ Buprenorphine can block the I_{HERG} channel but with a much lesser potency when compared with methadone, and the clinical relevance of this mild blockage seems to be almost irrelevant.²⁵ This relation between replacement therapy opioids is also seen in the clinic, where buprenorphine is less likely to increase QT intervals than methadone or LAAM.²⁹ Buprenorphine impact on QT intervals may become significant if concentrations become very high. The contribution of buprenorphine metabolites to hERG blockade is unknown.²⁹

Source: [Summary Expert Report](#)

Indivior conducted 2 nonclinical Good Laboratory Practices (GLP)-compliant toxicity and toxicokinetic studies in beagle dogs that also evaluated the cardiovascular safety of buprenorphine. The results from these studies demonstrated a lack of hERG blockade although both studies had initial Day 1 QTc prolongation. In a 2-week study (INLS-C100-63-15), a buprenorphine pro-drug was administered by oral gavage at doses of 1.2 to 12.6 mg/kg/day of buprenorphine hemiadipate for 14 consecutive days. Electrocardiography results showed a lengthening of the mean QT and QTc intervals at the Day 1 post-dose interval. The magnitude of the QTc interval change exceeded the 10% change seen in the Japanese QT PRODACT telemetry studies in dogs of medications known to cause QT prolongation in people⁴⁸ and ranged from 10.23 to 14.84%. Toxicokinetics results showed buprenorphine exposure levels with a C_{max} of 93.4 and 63.2 ng/mL (an order of magnitude higher than levels achieved with SUBOXONE) in males and females, respectively, in the highest dose group on Day 1. In the second study (INLS-C106-16), buprenorphine HCl + naloxone was administered in 6 sublingual films at a dose of 48 mg + 12 mg/day for 28 consecutive days. Electrocardiography confirmed findings noted in the initial study. A lengthening of the mean QT and QTc intervals was also observed on the Day 1 post-dose interval. The magnitude of the QTc interval change exceeded the 10% change seen in the Japanese QT PRODACT telemetry studies in dogs and ranged from 13.48 to 15.22%. Toxicokinetics results showed buprenorphine exposure levels that ranged from a C_{max} of 137 to 161 ng/mL (an order of magnitude higher than levels achieved with SUBOXONE) in males and females combined. Although the exact mechanism cannot be determined within the scope of either study and buprenorphine is known to have mild hERG blocking properties that can be associated with QTc prolongation, 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 (INLS-C100-63-15) or at Week 4 (INLS-C106-16), the board-

certified cardiologist for both studies determined that it was unlikely that the QTc prolongation noted at Day 1 was 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. Reduced activity, tremors and vocalisation were noted in all test article administered groups in both studies on Day 1. In addition, impaired neurological or neurobehavioral responses (e.g., ataxia or gait abnormalities) were noted in some groups. Gastrointestinal findings (emesis, vomiting, few or absent faeces, discoloured and watery faeces) were also noted at a higher incidence rate during the first week of the study. These clinical signs and QT/QTc changes were not present at the subsequent ECG collection at Day 14 or Week 4, lending further support to the theory that transient changes in autonomic tone are secondary to the acute administration of buprenorphine.^{15,4}

Source: [Summary Expert Report](#)

3.4 PREVIOUS CLINICAL EXPERIENCE

A through QT (tQT) study referenced in the US Prescribing Information (USPI) for BUTRANS®³⁴ (transdermal buprenorphine by Purdue Pharma) demonstrated no clinically meaningful effect at a dose of 10 µg/hour; however, a BUTRANS dose of 40 µg/hour (given as 2 BUTRANS 20 µg/hour Transdermal Systems) was observed to prolong mean QTc by a maximum of 9.2 (90% CI: 5.2-13.3) msec. Subsequently, NORSPAN®³⁶ (transdermal buprenorphine by Mundipharma Pty Limited, partner of Purdue Pharma) adopted similar language. The maximum BUTRANS dose is 20 µg/hour due to the risk of QTc interval prolongation, (b) (4)

Conversely, there is no mention of QT prolongation in the Summary of Product Characteristics (SmPC) for BUTRANS⁴³ 5 µg/hour, 10 µg/hour and 20 µg/hour and TRANSTEC®⁴⁵ (transdermal buprenorphine by Grünenthal GmbH), available in 35, 52.5 and 70 µg/hour.

As referenced in the USPI for BELBUCA®³² (buprenorphine buccal film by Endo Pharmaceuticals), QTc prolongation was observed in clinical trial settings. Of the 1,590 patients that were treated with BELBUCA in controlled and open-label chronic pain trials at doses up to 900 µg every 12 hours, 2% demonstrated a prolongation of QTc to a post-baseline value between 450 - 480 msec during therapy. QT prolongation as a common side effect is also referenced in SmPCs for sublingual buprenorphine tablets by Actavis UK Ltd⁴², and Sandoz Ltd (PREFIBIN®⁴⁴). However, the Product Information for PROBUPHINE®³⁵ (subdermal buprenorphine implant by Braeburn Pharmaceuticals), the latest approved buprenorphine containing product (BCP) for maintenance treatment of opioid use disorder (OUD), does not indicate that buprenorphine is associated with QT prolongation.

Sublingual buprenorphine tablets and film (SUBOXONE/SUBUTEX®), when administered for the treatment of OUD at recommended target dose of 16 mg/day, provide five-fold greater relative systemic exposure of buprenorphine as compared to BUTRANS 20 µg/hour (Sessler 201540).

Source: [Summary Expert Report](#)

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of RBP-6000's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor performed concentration–QT analysis from ECG data collected from pooled studies listed in Table 2 below. Based on this analysis the sponsor concluded that there was no relationship between buprenorphine concentration and QTc prolongation. However, we do not consider the concentration – QT analyses appropriate for this submission for reasons discussed in Section 1.2, and the analysis of the data submitted by the sponsor is therefore focused on categorical analysis and assessment of cardiac safety.

4.2 CONCENTRATION-QT ANALYSIS

4.2.1 Title

Concentration-QT Analysis for RBP-6000 Using Plasma Concentration and ECG Data Pooled from Studies RB-US-10-0011, RB-US-11-0020, RB-US-12-0005, RB-US-13-0001, and RB-US-13-0006

4.2.2 Protocol Number

Report 2344-001

4.2.3 Study Dates

14 March 2017

4.2.4 Objectives

- To evaluate whether there is a concentration-related effect of buprenorphine and norbuprenorphine on QT interval after accounting for the effect of relevant concomitant medications and illicit drug use on HR and/or QT in opioid-dependent subjects.
- To predict the concentration-related effects of buprenorphine on QTc interval at therapeutic and supra-therapeutic concentration levels.

4.2.5 Study Description

4.2.5.1 Design

Matching buprenorphine and norbuprenorphine plasma concentrations and 12-lead electrocardiograms (ECGs) were pooled across clinical studies conducted with RBP-6000 in opioid-dependent patients. Concentration-QT models were developed to describe the effects of buprenorphine and norbuprenorphine on corrected QT (QTc) interval, after accounting for the effect of relevant concomitant medications and illicit drug use on heart rate (HR) and/or QT in opioid-dependent patients. Data from the following studies were included in the analysis:

RB-US-10-0011:

Matched concentrations and single 12-lead ECG measurements (110 samples) from 12 patients who received a single SC injection of RBP-6000 containing 20 mg buprenorphine.

RB-US-11-0020: Matched concentrations and single 12-lead ECG measurements (767 samples) from 48 patients who received a single SC injection of 50 mg, 100 mg or 200 mg RBP-6000 (cohorts 1-3), or a single SC injection of 100 mg RBP-6000 following 7 consecutive days on SUBOXONE SL tablets to achieve a stable dose of 12 mg once daily (QD) (cohort 4).

RB-US-12-0005: Matched concentrations and single 12-lead ECG measurements (1241 samples) from 122 patients where 87 patients received repeated SC injections of RBP-6000 following induction and stabilization on various doses of SUBUTEX SL tablets, and 35 patients received SUBUTEX SL tablets alone. Stable doses of SUBUTEX SL tablets ranged between 8 and 24 mg depending on the dose cohort. RBP-6000 was given repeated (≥ 4) SC injections of 50 mg, 100 mg, 200 mg or 300 mg of buprenorphine separated by 28 days (Q28D).

RB-US-13-0006: Matched concentrations and single 12-lead ECG measurements (543 samples) from 66 patients, where 46 patients received a single SC injection of 300 mg RBP-6000 with either low, intermediate or high molecular weight of ATRIGEL polymer, following induction and dose stabilization with SUBOXONE SL film to achieve a stable dose of 12 mg QD. Twenty patients received SUBOXONE SL film alone.

RB-US-13-0001: Matched concentrations and single or triplicate 12-lead ECG measurements collected with and without Holter monitoring (9264 samples) from 866 patients were included in the analysis, where 437 patients have matched screening records but were not randomized and 429 patients were randomized to receive the following treatments:

- 300 mg/100 mg: 2 SC injections of 300 mg RBP-6000 Q28D (± 2 days) followed by 4 SC injections of 100 mg RBP-6000 Q28D (± 2 days)(165 patients),
- 300 mg/300 mg: 6 SC injections of 300 mg RBP-6000 Q28D (± 2 days) (174 patients),
- Placebo: volume-matched to 300 mg/100 mg group or 300 mg/300 mg group (90 patients).

Patients were inducted using SUBOXONE SL film for 3 days, followed by 4- to 11-day SUBOXONE SL film dose adjustment at doses ranging from 8 to 24 mg QD. SUBOXONE SL film was tapered in patients after amendment of study protocol (Day 1: 6 mg, Days 2 and 3: 4 mg, Days 4 and 5: 2 mg).

Table 2: Studies included in Concentration-QT Analysis

Study #	Patient Population	Study Design	Dose and Dosing Regimen	Blood Sample and 12-lead ECG Collection (prior to drug or when collected at the same time)*
RB-US-10-0011	Opioid-dependent subjects 12 enrolled and received at least one dose 6 completed	A Single-Dose, Open-Label Study of Depot Buprenorphine (RBP-6000) in Opioid-Dependent Individuals Inpatient: Days -2 to 30 Outpatient: Days 31 to 120	20 mg single dose SC 2 hour fast prior to dosing	Matched blood samples and single 12-lead ECG measurements were collected on Day 1 at 3 hr & 12 hrs post dose and Days 2, 3, 8, 14, 25-30 (prior to methadone and/or 4 hrs post methadone dose), 32, 57, 85, and 120. Day -2, Day 1 predose, and Screening ECG can be considered matched to a CONC=0, only if UDS and self-report were negative for buprenorphine. ECGs were single non-Holter readings.
RB-US-11-0020	Opioid-dependent subjects 51 enrolled and received at least one dose 35 completed	A Multicenter, Open-Label, Single Ascending-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Depot Buprenorphine (RBP-6000) in Opioid-Dependent Subjects Inpatient: Days -2 to 21 for cohorts 1-3 and days -9 to 21 for cohort 4	Cohorts 1-3: RBP-6000 50 mg, 100 mg, or 200 mg) Cohort 4: SUBOXONE 8 mg on Day -7, then 12 mg QD for 6 days followed by RBP-6000 100 mg	Matched blood samples and single 12-lead ECG measurements were collected on Days 1 at 3 hr and 12 hrs), 2, 3, 7, 14, 21, 35, 42, 63, 84, 112, and 150 and if subjects received methadone (4 hrs post methadone dose each day).
Study #	Patient Population	Study Design	Dose and Dosing Regimen	Blood Sample and 12-lead ECG Collection (prior to drug or when collected at the same time)*
RB-US-13-0006	Opioid-dependent subjects 47 enrolled 36 completed	A Single-Center, Randomized, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Depot Buprenorphine (RBP-6000) Using Poly (DL-lactide-co-glycolide) Polymer of Two Different Molecular Weights (Low and High Molecular Weights as Test Treatments) in Comparison to Intermediate Molecular Weight (Reference Treatment) in Treatment-Seeking Subjects with Opioid Use Disorder Inpatient: Day -9 to Day 3 Outpatient: Day 4 to Day 57	SUBOXONE run-in starting on Day -8, stabilization period to reach 12 mg QD by Day -5, continued on dose up until Day -1 Day 1 RBP-6000 300 mg 2 hour fast prior to RBP-6000 dosing	Matched blood samples and 12-lead ECG measurements were taken on Day 1 (pre-dose and 12), 2 (24 and 36 hr), Day 3 (48 hrs), Days 4, 6, 14, 27, and 57 Screening ECG can be considered matched to a CONC=0, only if UDS and self-report were negative for buprenorphine. ECGs were single non-Holter readings
RB-US-13-0001	Opioid-dependent subjects 470 subjects planned to be randomized 1:1:1 to 300 q28 x 2 plus 100 q28 x 4, 300 q28d x 6, or placebo after receiving a run-in treatment with SUBOXONE	A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy, Safety, and Tolerability of Multiple Subcutaneous Injections of Depot Buprenorphine (RBP-6000 [100 mg and 300 mg]) Over 24 Weeks in Treatment-Seeking Subjects with Opioid Use Disorder Inpatient: none Outpatient: all visits were outpatient visits	SUBOXONE run-in 2 mg/0.5 mg to 24 mg/6 mg x 3 days for induction followed by a 4 to 11-day dose adjustment. Randomized after at least 7 days of SUBOXONE treatment. Then taper SUBOXONE (following protocol amendment only): Day 1: 6 mg Day 2: 4 mg Day 3: 4 mg Day 4: 2 mg Day 5: 2 mg	Matched blood samples and single 12-lead ECG measurements were taken on Days -1, 8, 15, 22, 36, 43, 50, 64, 71, 78, 92, 99, 106, 120, 127, 134, 148, 155, 162, 169, and 197 Holter ECG measurements available on dosing days (Days 1, 2, 29, 30, 57, 58, 85, 86, 113, 114, 141, and 142) from pre-dose through 24 hrs and specific 12-lead ECG tracings of 10-second duration were extracted in triplicate prior to injection and 4 and 24 hrs post-dose;

Study #	Patient Population	Study Design	Dose and Dosing Regimen	Blood Sample and 12-lead ECG Collection (prior to drug or when collected at the same time) ^a
RB-US-11-0020 (Continued)		Outpatient: Days 21 to 84 (which could be extended if sustained buprenorphine concentrations still present)	2 hour fast prior to RBP-6000 dosing	Days -9 (cohort 4 only), -2, and Day 1 predose (from cohorts 1 to 3 only) and Screening (from all cohorts) ECG can be considered matched to a CONC=0, only if UDS and self-report were negative for buprenorphine. ECGs were single non-Holter readings
RB-US-12-0005	Opioid-dependent subjects 89 subjects received SUBUTEX + RBP-6000 35 subjects received only SUBUTEX	An Open-Label, Multicenter, Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics, Efficacy Markers, and Opioid Receptor Availability of Subcutaneous Injections of Depot Buprenorphine (RBP-6000) in Treatment Seeking Opioid-Dependent Subjects Inpatient: Days -13 to 3, Days 28 to 31, Days 56 to 59, Days 84 to 87, Days 112 to 115 (cohort 6 only), and Days 140 to 143 (cohort 6 only) Outpatient: Days 7 to 26, Days 31 to 56, Days 59 to 85, Days 87 to 113, Days 115 to 141 (cohort 6 only), and Days 143 to 169 (cohort 6 only)	SUBUTEX SL 13-day run-in 8, 12, 14, or 24 mg or 8-24 mg—stable dose by Day -5 Repeated doses (24 injections) of RBP-6000 SC 50, 100, 200, and 300 mg 2 hour fast prior to RBP-6000 dosing	Matched blood samples and 12-lead ECG measurements were taken on Day -5, 1 (at pre-dose ^d and 12 hrs), 3, 29 (2 and 12 hrs), 31, 57 (pre-dose and 12 hrs), 59, 85 (pre-dose and 12 hrs), 87, and 141 for cohorts 1-5 Cohort 6 had more dosing days planned and additional matched PK and ECG measurements on Days 113 (pre-dose and 12 hrs), 115, 141 (pre-dose and 12 hrs), 143, and 197 Screening (from all cohorts) ECG can be considered matched to a CONC=0, only if UDS and self-report were negative for buprenorphine. ECGs were single non-Holter readings
Study #	Patient Population	Study Design	Dose and Dosing Regimen	Blood Sample and 12-lead ECG Collection (prior to drug or when collected at the same time) ^a
RB-US-13-0001 (Continued)			On Day 1 subjects were randomized to the following treatments: 300 mg/300 mg: RBP-6000 SC 300 mg x 6 injections Q28D 300 mg/100 mg: RBP-6000 SC 300 mg x 2 injections followed by 100 mg x 4 injections Q28D Cohort 3: volume matched placebo SC injections x 6 ^b Fed/fast at dosing unknown	PK samples were taken at 1 and 4 hrs post-dose on dosing days Screening ECG can be considered matched to a CONC=0, only if UDS and self-report were negative for buprenorphine Placebo ECGs can be considered matched to a CONC=0 only ≥14 days after first dose. Holter data on study dosing days were manually read and included triplicate readings. All other ECGs were non-Holter readings in triplicate (at screening) or as a single reading (for all others)

^a Additional blood samples or ECG measurements may have been collected, but only simultaneous measurements were used in the analysis.

^b Placebo data cannot be used before Day 14 because of the SUBOXONE run-in and lack of PK samples. Values ≥ Day 14 were assumed to have concentrations of buprenorphine and norbuprenorphine equal to 0.

^c 3 hr ECG data matched with either the 2 hr or 4 hr blood sample, depending on which was closer in time to the actual collection of the ECG

^d Predose ECG and buprenorphine data on day 1 can only be matched if there is a quantifiable buprenorphine concentration

Source: Study report 2344-001, Appendix 1, Table 4, page 44/200

4.2.5.2 Controls

Only study RB-US-13-0001 included placebo treatment arm. None of the studies included a positive control.

4.2.5.3 Blinding

RBP-6000 was administered in an open-label manner in all studies, except study RB-US-13-0001.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

RBP-6000 included regime single doses of 20 mg, 50 mg, 100 mg and 200 mg and repeated doses of 50 mg, 100 mg, 200 mg and 300 mg Q28D. Below listed doses provided for each study.

RB-US-10-0011:

20 mg single dose SC (2 hour fast prior to dosing).

RB-US-11-0020:

Cohorts 1-3: RBP-6000 50 mg, 100 mg, or 200 mg

Cohort 4: SUBOXONE 8 mg on Day - 7, then 12 mg QD for 6 days followed by RBP-6000 100 mg 2 hour fast prior to RBP-6000 dosing.

RB-US-12-0005:

SUBUTEX SL 13-day run-in 8, 12, 14, or 24 mg or 8-24 mg - stable dose by Day -5
Repeated doses (≥ 4 injections) of RBP-6000 SC 50, 100, 200, and 300 mg 2 hour fast prior to RBP-6000 dosing.

RB-US-13-0006:

SUBOXONE run-in starting on Day -8 , stabilization period to reach 12 mg QD by Day -5, continued on dose up until Day -1 Day 1 RBP-6000 300 mg 2 hour fast prior to RBP-6000 dosing

RB-US-13-0001:

SUBOXONE run-in 2 mg/0.5 mg to 24 mg/6 mg x 3 days for induction followed by a 4 to 11-day dose adjustment. Randomized after at least 7 days of SUBOXONE treatment. Then taper SUBOXONE (following protocol amendment only):

- Day 1: 6 mg
- Day 2: 4 mg
- Day 3: 4 mg
- Day 4: 2 mg
- Day 5: 2 mg

On Day 1 subjects were randomized to the following treatments:

- 300 mg/300 mg: RBP-6000 SC 300 mg x 6 injections Q28D
- 300 mg/100 mg: RBP-6000 SC 300 mg x 2 injections followed by 100 mg x 4 injections Q28D

Cohort 3: volume matched placebo SC injections x 6^b Fed/fast at dosing unknown

4.2.6.2 Sponsor's Justification for Doses

The dose studied in the pivotal trial is the maximum tolerated and highest proposed clinical dose of 300 mg RBP-6000 administered as a subcutaneous injection every 28 days.

Reviewer's Comment: Acceptable to cover the therapeutic exposures, but not adequate to waive the requirement for inclusion of a positive control and as such the study does not support excluding small mean changes in the QTc interval.

4.2.6.3 Instructions with Regard to Meals

Not applicable.

4.2.6.4 ECG and PK Assessments

An overview of ECG/PK assessment is included in Table 2.

Reviewer's Comment: Acceptable, the ECG collection in the pivotal efficacy study included 24-h holter collection following each dose with an ECG extraction in triplicate at predose, 4 h post-dose and 24 h post-dose, covering the expected T_{max} . With regards to the 24 h time-point, the data for this time-point was not available for all patients, and an information request was sent to the sponsor. The sponsor responded (Seq [0025](#)), that the 12-lead ECG was not required per protocol at the injection visits, despite the following statement in the protocol "If, at the 24-hour post-injection visit, the patient returned without the Holter monitor, a 12-lead standard ECG was obtained."

4.2.6.5 Baseline

For all studies, the sponsor used the QTc values on screening day as baseline, where the patients might have been receiving other buprenorphine containing products. For a further discussion on the issue of baseline, please see section 5.2.

4.2.7 ECG Collection

Single 12-lead ECGs were measured in all studies.

In Study RB-US-13-0001, a combination of triplicate ECGs at Screening, single 12-lead ECGs on non-dosing days, and triplicate readings from Holter monitoring on dosing days were collected. When Holter monitoring was available, specific 12-lead ECG tracings of 10-second duration were extracted in triplicate prior to SC injection and 4 and 24 hrs post SC injection on each dosing day. Only Holter and non-Holter data from Study RB-US-13-0001 were centrally read; non-Holter ECGs data from all other studies were reviewed by the Investigator at the site for any abnormalities.

4.2.8 Sponsor's Results

The results of the sponsor's analysis suggest no relationship between buprenorphine concentration and baseline- and placebo-adjusted change from baseline in QTc.

Reviewer's comment: As stated in section 1.2, we believe there are several issues with pooling studies for the analyses. Owing to these concerns, we do not deem the results from the sponsor's analyses acceptable.

4.2.8.1 Study Subjects

The full dataset included 11925 observations from 1114 subjects and the reduced dataset included 2210 observations from 1099 subjects.

RB-US-10-0011:

Opioid-dependent subjects 12 enrolled and received at least one dose 6 completed

RB-US-11-0020:

Opioid-dependent subjects 51 enrolled and received at least one dose 35 completed

RB-US-12-0005:

Opioid-dependent subjects 89 subjects received SUBUTEX + RBP- 6000
35 subjects received only SUBUTEX

RB-US-13-0006:

Opioid-dependent subjects 47 enrolled 36 completed

RB-US-13-0001:

Opioid-dependent subjects 470 subjects planned to be randomized 1:1:1 to 300 q28 x 2 plus 100 q28x 4, 300 q28d x 6, or placebo after receiving a run-in treatment with SUBOXONE

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

As noted in section 1.2, the data collected does not permit concentration-QTc analysis.

4.2.8.2.2 Assay Sensitivity

Not applicable.

4.2.8.2.3 Categorical Analysis

Outlier analysis for QTcF are shown in the tables below.

Table 3: Outlier analysis of 12-lead QTcF data from Phase 3 studies

Time point/ Category Baseline QTcF Intervals (msec)	13-0001 (Phase 3 DB)			13-0003 (Phase 3 OL)				All Phase 3 (13-0001 & 13-0003) Total RBP-6000 (N=848) n (%)
	RBP-6000 300/100 (N = 203) n (%)	RBP-6000 300/300 (N = 201) n (%)	PBO (N = 100) n (%)	Roll-over			De novo	
				RBP-6000 100 → RBP-6000 300/Flex (N=112) n (%)	RBP-6000 300 → RBP-6000 300/Flex (N=113) n (%)	PBO → RBP-6000 300/Flex (N=32) n (%)	RBP-6000 300/Flex (N=412) n (%)	
Number of Subjects with at least 1 postbaseline QTcF Measurements	199	200	97	112	113	32	412	843
Baseline QTcF Intervals (msec)								
≤ 450	198 (99.5)	197 (98.5)	96 (99.0)	112 (100.0)	112 (99.1)	32 (100.0)	407 (98.8)	834 (98.9)
> 450 to ≤ 480	1 (0.5)	3 (1.5)	1 (1.0)	0	1 (0.9)	0	5 (1.2)	9 (1.1)
> 480 to ≤ 500	0	0	0	0	0	0	0	0
> 500	0	0	0	0	0	0	0	0
Worst Post-baseline QTcF Intervals (msec)								
≤ 450	180 (90.5)	175 (87.5)	96 (99.0)	103 (92.0)	102 (90.3)	26 (81.3)	381 (92.5)	753 (89.3)
> 450 to ≤ 480	19 (9.5)	21 (10.5)	1 (1.0)	9 (8.0)	11 (9.7)	6 (18.8)	27 (6.6)	82 (9.7)
> 480 to ≤ 500	0	3 (1.5)	0	0	0	0	3 (0.7)	6 (0.7)
> 500	0	1 (0.5)	0	0	0	0	1 (0.2)	2 (0.2)
Change from Baseline in Worst Post-baseline QTcF Intervals (msec)								
> 30 to < 60	37 (18.6)	38 (19.0)	16 (16.5)	11 (9.8)	20 (17.7)	7 (21.9)	97 (23.5)	213 (25.3)
≥ 60	2 (1.0)	5 (2.5)	0	0	0	0	3 (0.7)	10 (1.2)

Notes: Individual study data are provided in the 13-0001 and 13-0003 columns. In the All Phase 3 column, total includes unique number of subjects exposed to RBP-6000 including data from subjects who participated in 13-0001 and did not roll-over to 13-0003, 13-0003 roll-over subjects (combining exposure to RBP-6000 across both 13-0001 and 13-0003) and 13-0003 de novo subjects.
Excludes ECGs not centrally read.

Percentage is computed based on the number of subjects with at least 1 postbaseline QTcF measurement as a denominator from the respective columns.
Study 13-0001: All subjects in the RBP-6000 treatment groups were scheduled to receive 2 injections of RBP-6000 300 mg. Subjects in the 300/100 and 300/300 treatment groups were scheduled to then receive up to 4 injections of RBP-6000 100 mg or up to 4 injections of RBP-6000 300 mg, respectively.

Study 13-0003:

- Roll-over subjects: The treatment groups represent the treatment in Study 13-0001 → treatment in Study 13-0003.
- RBP-6000 300/Flex: Represents treatment with an initial injection of RBP-6000 300 mg followed by up to 5 additional injections using flexible dosing with either RBP-6000 300 mg or RBP-6000 100 mg as deemed appropriate by the investigator.
- All de novo subjects received an initial injection of RBP-6000 300 mg followed by up to 11 additional injections using flexible dosing with either RBP-6000 300 mg or RBP-6000 100 mg as deemed appropriate by the investigator.

Source: [Summary of Clinical Safety](#) – Table 123 on Page 242

Table 4: Outlier analysis of 12-lead QTcF data from Study 12-0005

Time point/ Category	Cohort 1 SUBUTEX + RBP-6000 50 mg (N=15) n (%)	Cohort 2 SUBUTEX + RBP-6000 100 mg (N=15) n (%)	Cohort 3 SUBUTEX + RBP-6000 200 mg (N=15) n (%)	Cohort 4 SUBUTEX + RBP-6000 100 mg (N=15) n (%)	Cohort 5 SUBUTEX + RBP-6000 200 mg (N=15) n (%)	Cohort 6 SUBUTEX + RBP-6000 300 mg (N=14) n (%)	Total RBP-6000 (N=89) n (%)
Number of Subjects with at least 1 postbaseline QTcF Measurements	15	15	15	15	15	14	89
Baseline QTcF Intervals (msec)							
≤ 450	13 (86.7)	15 (100.0)	14 (93.3)	15 (100.0)	15 (100.0)	14 (100.0)	86 (96.6)
> 450 to ≤ 480	2 (13.3)	0	1 (6.7)	0	0	0	3 (3.4)
> 480 to ≤ 500	0	0	0	0	0	0	0
> 500	0	0	0	0	0	0	0
Worst Post-baseline QTcF Intervals (msec)							
≤ 450	11 (73.3)	14 (93.3)	14 (93.3)	13 (86.7)	11 (73.3)	13 (92.9)	76 (85.4)
> 450 to ≤ 480	4 (26.7)	1 (6.7)	1 (6.7)	2 (13.3)	3 (20.0)	1 (7.1)	12 (13.5)
> 480 to ≤ 500	0	0	0	0	0	0	0
> 500	0	0	0	0	1 (6.7)	0	1 (1.1)
Change from Baseline in Worst Post-baseline QTcF Intervals (msec)							
> 30 to < 60	1 (6.7)	4 (26.7)	2 (13.3)	3 (20.0)	5 (33.3)	2 (14.3)	17 (19.1)
≥ 60	0	0	0	0	1 (6.7)	0	1 (1.1)

Notes: Total includes UNIQUE number of subjects exposed to RBP-6000. Only locally read ECGs were included in this summary. All subjects were dosed with SUBUTEX SL tablets containing 8 mg to 24 mg on Day -13 to Day -1. Subjects subsequently received RBP-6000 containing 50, 100, 200 or 300 mg of buprenorphine every 28 days. Subjects in Cohorts 1 to 5 received up to 4 injections of RBP-6000 in the main study. Subjects in Cohort 6 received up to 6 injections of RBP-6000 in the main study.

Cohort 1: Stabilised on SUBUTEX SL tablet 8 mg then RBP-6000 containing 50 mg buprenorphine.
 Cohort 2: Stabilised on SUBUTEX SL tablet 12 mg then RBP-6000 containing 100 mg buprenorphine
 Cohort 3: Stabilised on SUBUTEX SL tablet 24 mg then RBP-6000 containing 200 mg buprenorphine.
 Cohort 4: Stabilised on SUBUTEX SL tablet 8 mg then RBP-6000 containing 100 mg buprenorphine
 Cohort 5: Stabilised on SUBUTEX SL tablet 14 mg then RBP-6000 containing 200 mg buprenorphine
 Cohort 6: Stabilised on a dose of SUBUTEX SL tablet between 8 and 24 mg then RBP-6000 containing 300 mg buprenorphine.

Source: [Summary of Clinical Safety – Table 143 on Page 247](#)

Table 5: Outlier analysis of 12-lead QTcF data from Study 13-0002

Time point/ Category	13-0002 (OB)
	SUBOXONE SL film + RBP-6000 300 mg (N=39) n (%)
Number of Subjects with at least 1 post baseline QTcF Measurements	39
Baseline QTcF Intervals (msec)	
≤ 450	39 (100.0)
> 450 to ≤ 480	0
> 480 to ≤ 500	0
> 500	0
Worst Post Baseline QTcF Intervals (msec)	
≤ 450	37 (94.9)
> 450 to ≤ 480	2 (5.1)
> 480 to ≤ 500	0
> 500	0
Change from Baseline in Worst Post baseline QTcF Intervals (msec)	
> 30 to < 60	4 (10.3)
≥ 60	0
All subjects were dosed with SUBOXONE SL film containing 8 mg to 24 mg on Day -14 to Day -1. Subjects subsequently received RBP-6000 containing 300 mg of buprenorphine on Day 1 (n = 39) and on Day 29 (n = 30). Only Locally read ECGs should be included in this summary. Table_4_92.sas	
2017-05-01	

Source: [Integrated Summary of Safety Tables & Figures – Table 4.92 on Page 2222,](#)

2223

Outlier analysis of 12-lead QTcF data from Study 13-0006

Time point/ Category	13-0006 (MW)
	SUBOXONE SL + RBP-6000 300 mg (N=47) n (%)
Number of Subjects with at least 1 post baseline QTcF Measurements	47
Baseline QTcF Intervals (msec)	
≤ 450	47 (100.0)
> 450 to ≤ 480	0
> 480 to ≤ 500	0
> 500	0
<small>All subjects were stabilised on SUBOXONE SL prior to receiving a single SC injection of RBP-6000 containing 300 mg buprenorphine. The 3 MW treatment groups (PLGH A=9 kDa PLGH polymer [low MW]; PLGH B=17 kDa PLGH polymer [high MW]; PLGH C=14 kDa PLGH polymer [intermediate MW]) were combined. Only Locally read ECGs should be included in this summary.</small>	
<small>Table_4_95.sas</small>	<small>2017-05-01</small>

Source: [Integrated Summary of Safety Tables & Figures](#) – Table 4.95 on Page 2287

Reviewer’s Comments: We provided our independent analysis in Section 5, which is based on the raw ECG data (without averaging) collected in study RB-US-13-0001.

4.2.8.3 Safety Analysis

QT Prolongation Categorical Outliers

Narratives of for patients with QTc >480 ms or ΔQTc >60 ms were extracted from summary of clinical safety and presented below.

Phase 3 Study 13-0001: Seven patients, all in the active treatment groups, had changes from baseline in QTcF of ≥ 60 ms at any time: 2/199 patients (1.0%) in the 300/100 mg group and 5/200 patients (2.5%) in the 300/300 mg group (Table 3).

- One patient had QTcF > 500 ms and change from baseline >60 ms. Patient (b) (6), a 33-year-old white male, received a total of 6 SC injections of RBP-6000. The patient had an ongoing medical history of hypertension. No concomitant cardiac medications were reported. The patient had an overall interpretation on ECG of abnormal CS at Week 11 on (b) (6), 13 days after Injection #3; no other ECGs had this overall interpretation through Week 25. Overall interpretation at baseline had been abnormal NCS. The patient tested non-negative by UDS for amphetamine on this same date of (b) (6). On this same date, a TEAE of electrocardiogram QT prolonged assessed as moderate and related to study treatment was reported. QTcF was 476 ms and 503 ms (this value was unscheduled) on this date; at baseline QTcF was 423 ms. The outcome was recovered on (b) (6). The patient completed the study.
- Patient (b) (6), a 40-year-old white male, received a total of 5 SC injections of RBP-6000. No cardiac medical history or concomitant cardiac medications were reported. The patient had an overall interpretation on ECG of abnormal CS at their last visit on (b) (6), approximately 2 months after their final dose (Injection #5) was received; no other ECGs had this overall interpretation prior to this one. Overall interpretation at baseline had been normal. No UDS test results were reported for (b) (6); however, the patient had tested non-negative multiple times throughout the study for cocaine metabolite with the last UDS test reported non-negative on (b) (6). Results from TLFB on (b) (6) were non-negative for cocaine. On this same date, a TEAE of

- electrocardiogram QT prolonged (described as long QT interval) assessed as mild and not related to study treatment was reported. QTcF was 488 ms on this date; at baseline QTcF was 419 ms. The event was ongoing with an outcome of not recovered. The patient discontinued the study after Injection #5 due to a TEAE of formication (described as a feeling of bugs crawling on skin).
- Patient (b) (6), a 32-year-old white female, received a total of 6 SC injections of RBP-6000. No cardiac medical history was reported. The patient was taking concomitant clonidine and hydrochlorothiazide for hypertension. The patient had an overall interpretation on ECG of abnormal CS at Week 11 on (b) (6), 14 days after Injection #3; no other ECGs had this overall interpretation through Week 25. Overall interpretation at baseline had been abnormal NCS. The patient tested non-negative by UDS and by TLFB report for cocaine metabolite and cocaine on the same date of (b) (6). On this same date, a TEAE of electrocardiogram QT prolonged (increased QTcF) assessed as mild and not related to study treatment was reported. QTcF was 498 ms on this date; at baseline QTcF was 428 ms. The outcome was recovered on (b) (6). The patient completed the study.
 - Patients (b) (6) had an overall interpretation of the ECG of normal on the day of QTcF elevation. No TEAEs potentially pertaining to ECGs were reported for these patients during the study. No additional confounding factors in medical history or concomitant medications were identified. Two of these 3 patients tested non-negative by UDS and/or TLFB results for cocaine or cocaine metabolite on the same day that their QTcF was \geq 60 ms from baseline.

Open Label Study 13-0003: One patient had a post-baseline QTcF value >500 ms (Table 3). This patient and 2 additional patients had changes from baseline in QTcF ≥ 60 ms.

- For Patient (b) (6) was a 31-year-old female with ECG findings of QTcF increase of > 60 ms compared with baseline at Week 25 (Day 169) 1 hour post injection with a maximum change from baseline (423 ms of 89 ms (512 ms). The patient reported no relevant medical history and baseline ECG findings were within the normal range; however, the patient had a positive drug use history of cocaine. Additionally, this patient tested positive by UDS for benzoylecgonine (cocaine metabolite) on the same day (Day 169) as well as through Week 9 to Week 33. Patient had been treated with fluoxetine since (b) (6) (can reduce heart rate).
- Patient (b) (6) was a 28-year-old male with ECG findings of QTcF increased of > 60 ms compared with baseline at Week 19 (Day 127) and Week 21 (Day 142) which changed from a baseline QTcF finding of 352 ms to 415 ms on Day 127 and 413 ms on Day 142. The patient had no relevant cardiac history, however, the patient had a history of blood cholesterol increased that was ongoing at the time of this event. Additionally, the patient tested positive by UDS for amphetamine on the same day as well as screening through Week 33. No treatment leading to heart rate reduction was concomitantly used; however, the patient has been treated with ibuprofen 400 mg since (b) (6), and it

has been reported in the literature that ibuprofen may, in some cases, reduce heart rate.

- Patient (b) (6) was a 33-year-old male with ECG findings of QTcF increase of > 60 ms compared with baseline from Week 1 through Week 13, with a maximum change from baseline (363 ms) of 125 ms at Week 2 Day 8 (488 ms). Additionally, this patient tested positive by UDS for cannabinoids and/or amphetamine at Week 1 through Week 17. The patient did not receive any concomitant medication during his participation in the study.

Reviewer's Comments: The narratives for patients with notable QTc prolongation are confounded with non-negative urine tests for illicit drugs. Otherwise the patients do not appear to be taking prescribed drugs known to prolong the QTc interval.

Reviewer's evaluation of all the available ECG data, without averaging, from Study 13-0001 did detect 4 additional patients with QTc outliers: 3 patients >480 ms in the 300/100 dose group and 1 patient >480 ms in the 300/300 dose group. See Section 5.1 for independent analysis of the ECG data collected in Study 13-0001.

MAD 12-0005: Among patients who received both SUBUTEX and RBP-6000, 1 patient had a QTcF value > 500 ms that was also a > 60 ms change from baseline (Table 4).

- Patient (b) (6) was a 44-year-old black or African-American female. Her relevant medical history included opioid dependence (b) (6) and hepatitis C (b) (6). Ongoing relevant medications included hydroxyzine 100 mg QD for vertigo and anxiety (started on (b) (6)) and methocarbamol 750 mg as needed for musculoskeletal pain (started (b) (6)). On (b) (6) (Day 57) she received her third injection of RBP-6000 SC, containing 200 mg of buprenorphine. On Day 59 (b) (6) 48 hours after the third injection, the patient had a QTcF value of 586 ms. Her baseline ECG on (b) (6) was normal, with a QTcF value of 423 ms. Between screening and Day 59, all QTcF values were lower than 450 ms. An unscheduled ECG conducted 14 minutes after the 1 that showed QT prolongation, was normal (QTcF 382 ms). All subsequent ECGs during the study were also found normal. The patient was not bradycardic on Day 59. A UDS performed on Day 57 was positive for cocaine and opiates, however another 1 performed 2 days later (Day 59) was negative for cocaine. Laboratory tests conducted on (b) (6) showed no clinically relevant out-of-range haematological or chemistry values. The dose of RBP-6000 was not changed and the patient did not discontinue the study following this event. The patient completed the study on (b) (6).

Reviewer's Comment: A repeat ECG collected 14 minutes later did not confirm the QTcF value of 586 ms. Therefore, this outlier values may have been an anomaly.

Adverse Events Important to ICH E14 Guideline

No cases of Torsade de pointes, ventricular tachycardia or fibrillation were reported.

Six cases of syncope were reported: 1 of near syncope, 1 of vasovagal syncope, 2 of intermittent syncope and 2 of syncope not otherwise specified.

- Patient (b) (6) was a 39-year-old black or African-American female. Her relevant medical history included opioid dependence (b) (6), heart murmur (b) (6) and hepatitis C (b) (6). On (b) (6) at 9:05am she received her first and only RBP-6000 SC injection, containing 50 mg buprenorphine. On (b) (6), the patient experienced a syncope episode. The event was assessed as mild in severity and the outcome was reported by the investigator as recovered/resolved on the same day it started. On that day, the patient also presented with moderate opioid withdrawal. the patient did not discontinue the study following this event. Patient completed the study on (b) (6).
- Patient (b) (6) was a 32-year-old white (not Hispanic or Latino) male. His relevant medical history included opioid dependence (b) (6), polysubstance abuse (b) (6), constipation (b) (6) and elevated bilirubin (b) (6), all of which were ongoing. On (b) (6), he received his first RBP-6000 SC injection, containing 100 mg buprenorphine. On (b) (6), the patient experienced syncope which was intermittent in nature, mild in severity and recovered on (b) (6) with dose not changed. The first ECG performed at screening was considered abnormal (NCS) with nonspecific ST elevation and QTcF of 437 ms. On Day 1, ECG was normal. The last ECG (b) (6) performed before the AE of syncope was assessed as abnormal (NCS) with nonspecific ST elevation and QTcF of 407 ms. The patient did not discontinue the study following this event. The patient completed the study on (b) (6).
- Patient (b) (6) was a 22-year-old white (not Hispanic or Latino) female. Her relevant medical history included opioid dependence (b) (6), polysubstance abuse (b) (6), anxiety (b) (6), and seizure secondary to fluoxetine (reported only once in 2005). On (b) (6) she received an injection of RBP-6000 SC, containing 200 mg of buprenorphine. On (b) (6), the patient began experiencing a presyncopal state during 1 minute. An adverse event of tachycardia, mild in severity, was also reported as starting on (b) (6). The tachycardia recovered/resolved on (b) (6), per the investigator. An ECG performed on (b) (6) was considered normal and similar to the 1 performed at screening (b) (6).
- Patient (b) (6) was a 31-year-old white (Hispanic or Latino) female. Her ongoing relevant medical history included severe OUD (b) (6) and hepatitis C (b) (6). On (b) (6), she received SUBOXONE sublingual film 12 mg at 8:30 am. On (b) (6), the patient experienced a mild vasovagal syncope considered unrelated to SUBOXONE. This occurred in the context of an infection. No ECG was performed on the day the AE of vasovagal syndrome occurred. The patient completed the entire study with last visit on (b) (6).
- Patient (b) (6) was a 51-year-old white male. On (b) (6) (Day 1) he received his first injection of RBP-6000 SC, containing 300 mg of buprenorphine. After the injection, on the same day, the patient experienced a TEAE of syncope. An ECG performed on the same day was interpreted as normal and similar to the 1 performed at screening (b) (6). The event was assessed as mild in severity and recovered/resolved on the same day it occurred.

- Patient (b) (6) was a 25-year-old white (Hispanic or Latino) male. This patient was reported to have a TEAE of syncope on (b) (6) (Day 25). TEAEs of bradycardia and rectal bleeding were reported as starting on the same date. The syncope was assessed to be moderate in severity and the outcome was reported as recovered/resolved on the same day it occurred. The last 3 ECGs performed on (b) (6) were all reported as abnormal after an automated ECG interpretation, however no CS abnormality was found following a medical review of those 3 ECG strips. The QTcF values on those days were 404 ms, 407 ms, 405 ms respectively. The dose of the study drug was not changed.

Two cases of seizure were reported: 1 generalized seizure and 1 seizure not otherwise specified, both related to other medications or illicit drugs. Neither of these cases was considered related to study medication by the investigator.

- This 37-year-old, white, male patient with severe OUD was a roll-over participant in RB-US-13-0003 and received 5 injections of RBP-6000 at a dose of 300 mg subcutaneously on (b) (6). The patient withdrew consent to participate in the study due to relocation and was discontinued from the study on (b) (6). On (b) (6), the patient experienced an SAE of severe generalized tonic-clonic seizure (verbatim text: 2 generalized tonic-clonic seizures). On (b) (6), the patient was hospitalized due to severe generalized tonic-clonic seizures. It was reported that cocaine use and lack of sleep were the possible cause of the seizures. No action was taken with regard to RBP-6000 dosing as a result of the generalized tonic-clonic seizure.
- This 31-year-old, white, male patient with severe OUD was a de novo participant in RB-US-13-0003 and received 8 injections of RBP-6000 at a dose of 300 mg subcutaneously. On the evening of (b) (6) the patient experienced symptoms of an opioid overdose (verbatim text: accidental heroin overdose). He was administered 1 nasal dose of naloxone 4 mg by his fiancé. Later, the patient became unresponsive and exhibited seizure-like activity and was transported to the hospital where the seizure-like activity was noted to have self-resolved. On (b) (6), the SAE was considered resolved/recovered and the patient was discharged with no further complications. No action was taken with regard to RBP-6000 dosing as a result of the overdose. The SAE was considered by the investigator to be unrelated to RBP-6000 treatment.

Reviewer's Comments: None of the patients with syncope or seizure AEs experienced QTc prolongation.

Expert Cardiology Review of Holter ECG Recordings

The efficacy study included collection of holters at multiple visits, and all reported “ventricular runs” or “ventricular tachycardia”.

There were a total of 36 Holter recordings that were reported to have either idioventricular rhythm (6 Holters) or ventricular tachycardia (30 Holters). All events were nonsustained. The Expert Cardiologist confirmed that each of these Holters did in

fact demonstrate at least 1 episode of a nonsustained, wide complex tachycardia. While 1 or 2 may have been episodes of supraventricular tachycardia with aberration, the diagnoses in general appeared to be correct.

The prevalence of nonsustained ventricular tachycardia noted in this trial is not statistically different from the background prevalence of nonsustained ventricular tachycardia observed in healthy individuals. Nonsustained ventricular tachycardia has been reported that be present 1-5% of 24 hour Holter recordings performed in healthy volunteers (Min 2010 and Hingorani 2016). Thus, despite treatment with RBP-6000 (and often with concomitant use of illicit drugs), the prevalence of nonsustained ventricular tachycardia in RB-US-13-0001 (30 of 1403 Holters; 2.1%) was not higher than would be observed in a healthy subject population. Although the results of the Holters performed following the first dose of study medication are not available, the Holter data recorded in RB-US-13-0001 demonstrated no increase in the prevalence of ventricular arrhythmias.

Reviewer's Comment: Expert cardiologist did not report any clinically significant ventricular tachyarrhythmias based on evaluation of the 24-h Holter recordings at each dosing visit.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Not provided.

4.2.8.4.2 Exposure-Response Analysis

As discussed in the summary, the data collected does not support exposure-response analysis.

5 REVIEWERS' ASSESSMENT

The sponsor used QTcF and QTcB for evaluation of outliers.

5.1 STATISTICAL ASSESSMENTS

The statistical assessment focused on evaluation of absolute PR, QRS and QTcF outliers in the phase 3 study (RB-US-13-0001), as the study included two dose levels and placebo, and the results of this analysis is shown in Table 6 as well as change from baseline in QTcF. The results shown in Table 6 shows a similar proportion of PR and QRS outliers between the two treatment groups and placebo, and few QTcF outliers, which are discussed in section 4.2.8.3. Please note, that the numbers in reviewer's table differs from the analysis presented in the clinical summary of safety, as the reviewer did not average the ECG values by visit.

Table 6: Analysis of PR, QRS and QTcF outliers in RB-US-13-0001

	Placebo (n=99)	300/100 mg (n=202)	300/300 mg (n=201)
PR			
>220 ms	4 (4%)	8 (4%)	7 (3.5%)
QRS			
>110 ms	18 (18.2%)	42 (20.8%)	34 (16.9%)
QTcF			
>480 ms	0 (0%)	3 (1.5%)	4 (2.0%)
>500 ms	0 (0%)	0 (0%)	1 (0.5%)
ΔQTcF			
>30 ms	31 (31.3%)	62 (30.7%)	64 (31.8%)
>60 ms	0 (0%)	7 (3.5%)	9 (4.5%)

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

To explore the changes in QTc as it relates to exposure, the reviewer 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 results of the analysis by the reviewer is presented below in Figure 1. From this figure the following observations can be made:

- 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 visit, a mean Δ QTc 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.
- Consistent with the analysis presented in section 5.1 above, there were no QTc values exceeding 480 ms and no Δ QTc values exceeding 60 ms at the C_{max} for the 5th and 6th injection.
- A sensitivity analysis using data from the visit after the T_{max} was performed because of missing data at the T_{max} visit. This analysis confirmed the analysis using T_{max} . At this visit (day 148) a mean (upper 95% CI) Δ QTc of -0.8 ms (4.4 ms) was observed for placebo and 2.6 ms (5.8 ms) and 2.2 ms (5.2 ms) was observed for 300/100 and 300/300 mg respectively.

These data suggest an absence of a large difference in the QTc effect in the exposure range studied.

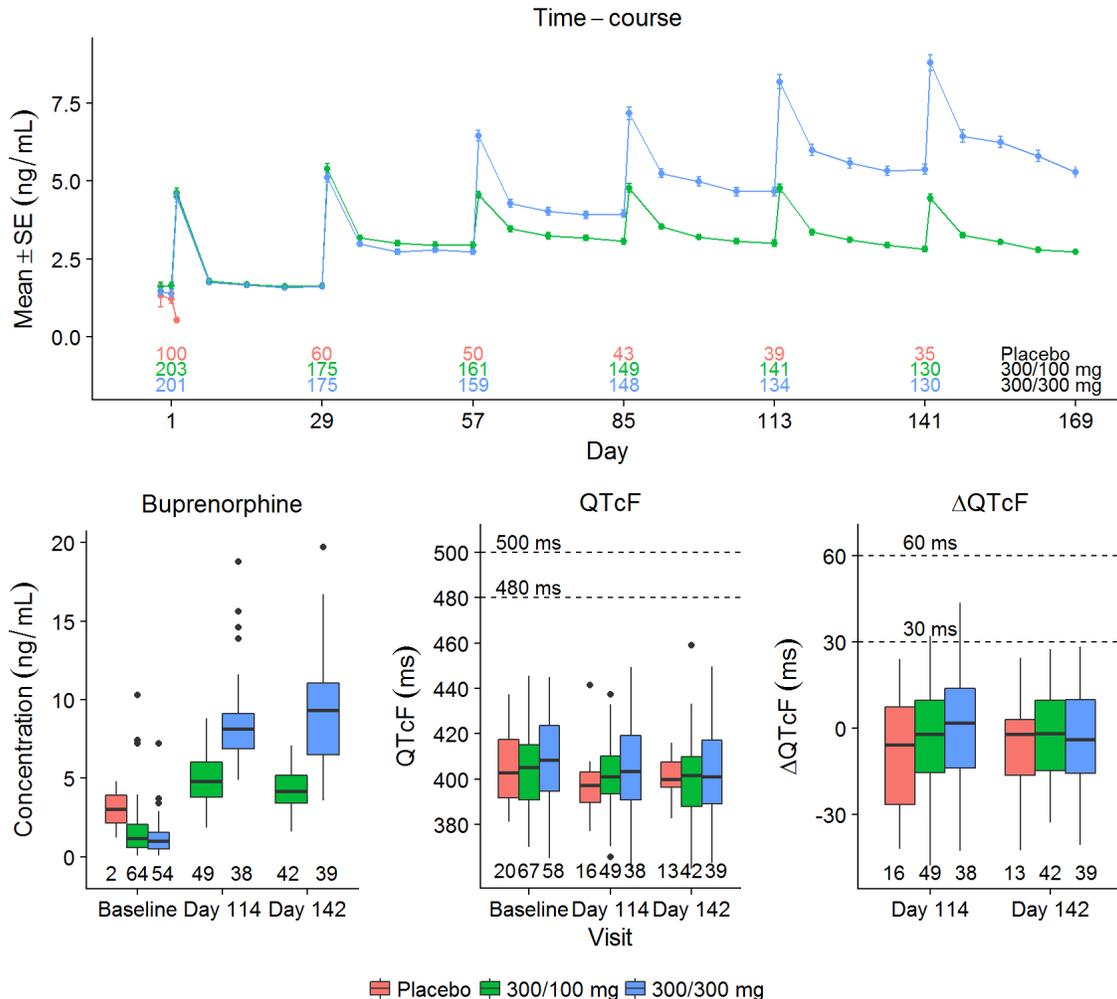


Figure 1: Evaluation of the buprenorphine concentrations over time (top panel) and comparison of the buprenorphine concentrations and QTc measurements at baseline and two visits at steady-state (bottom row). In the top row, data from 4 h post-dose is excluded and the mean is only included in the figure if more than 5 patients contributed to the mean. Additionally, the text in the bottom portion of top panel represents how many patients received a dose of RBP-6000 or placebo at any given visit. The panels in the bottom row represents: buprenorphine concentration (left panel), absolute QTc (middle panel) and Δ QTc (right panel) for patients with 24 h holter data (anticipated T_{max}) available after the 5th or 6th visit. The dashed lines in the middle and right panel represents QTc cutoffs used for outlier analysis. Lastly, the numbers below each boxplot represents the number of patients with available data. [Source: Reviewer's Analysis]

5.3 CLINICAL ASSESSMENTS

5.3.1 Safety assessments

See section 4.2.8.3 for a review of the QTc prolongation AEs.

5.3.2 ECG assessments

Only ECGs from Study RB-US-13-0001 were uploaded. Overall ECG acquisition and interpretation in this study appears acceptable.

5.3.3 PR and QRS Interval

No clinically relevant effects on the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	300 mg Subcutaneous (SC) Injection Once Monthly					
Maximum tolerated dose	Single Dose	300 mg SC Injection				
	Multiple Dose	300 mg SC Once Monthly Injection				
Principal adverse events	For the overall development program, the most common adverse events reported for RBP-6000 were drug withdrawal syndrome, headache, constipation, upper respiratory tract infection, nausea, and injection site reactions like injection site pain and pruritus. Relative to the known safety profile for buprenorphine, there were no unexpected safety findings and no new safety signals identified.					
Maximum dose tested	Single Dose	300 mg SC Injection				
	Multiple Dose	300 mg SC Once Monthly Injection				
Exposures Achieved at Maximum Tested Dose	Single Dose	Study	Dose	Geometric Mean (%CV)		
		Single Dose, Molecular Weight Study (RB-US-13-0006)	300 mg SC	C _{max} (ng/mL)	5.72 (27.0)	
				AUC _{last} (ng•h/mL)	1470 (51.4)	
	Multiple Dose	Study	Dose	Injection	Geometric Mean (%CV)	
		Multiple Dose Study, (RB-US-12-0005)	300 mg SC	1	C _{max} (ng/mL)	4.60 (29.8)
					AUC _{tau} (ng•h/mL)	1218.9 (30.7)
4			C _{max} (ng/mL)	9.38 (24.3)		
			AUC _{tau} (ng•h/mL)	3216.5 (13.3)		
<ul style="list-style-type: none"> In study RB-US-12-0005, assessment of steady-state of buprenorphine for the SC doses at 50 mg, 100 mg, 200 mg and 300 mg was carried out using Helmert's method using C_{trough} values. Steady-state for buprenorphine following multiple SC injections was achieved on or before Day 85 (Injection 4) for all dose levels, except for the 100 mg dose level. Further analysis of steady-state will be assessed as part of the population PK analysis of Phase 3 data. 						
Range of linear PK	Dose proportionality was assessed over the dose range of 50 to 300 mg in multiple ascending dose following the 1 st , 4 th or 6 th injection. Overall, the results show that buprenorphine plasma exposure increased slightly less than					

	proportionally, a 6-fold increase in dose resulted in approximately 5.1-fold and 5.2-fold increases in buprenorphine C_{max} and AUC_{tau} , respectively.																						
Accumulation at steady state	<ul style="list-style-type: none"> Accumulation ratios (Rac; geometric mean) for buprenorphine of overall AUC_{tau} and C_{max} following SC Injection 4 relative to Injection 1 ranged from 2.4 to 3.6 and 1.3 to 1.9, respectively. 																						
	Buprenorphine																						
		<table border="1"> <thead> <tr> <th></th> <th>Cohort 1 50 mg</th> <th>Cohort 2 100 mg*</th> <th>Cohort 3 200 mg*</th> <th>Cohort 4 100 mg*</th> <th>Cohort 5 200 mg*</th> <th>Cohort 6 300 mg</th> </tr> </thead> <tbody> <tr> <td>Rac(AUC_{tau})</td> <td>2.4 (37.5)</td> <td>2.7 (18.6)</td> <td>3.3 (26.9)</td> <td>3.3 (27.2)</td> <td>2.7 (30.5)</td> <td>3.6 (15.8)</td> </tr> <tr> <td>Rac(C_{max})</td> <td>1.3 (33.4)</td> <td>1.5 (34.1)</td> <td>1.7 (30.6)</td> <td>1.7 (35.3)</td> <td>1.5 (16.9)</td> <td>1.9 (23.1)</td> </tr> </tbody> </table>		Cohort 1 50 mg	Cohort 2 100 mg*	Cohort 3 200 mg*	Cohort 4 100 mg*	Cohort 5 200 mg*	Cohort 6 300 mg	Rac(AUC_{tau})	2.4 (37.5)	2.7 (18.6)	3.3 (26.9)	3.3 (27.2)	2.7 (30.5)	3.6 (15.8)	Rac(C_{max})	1.3 (33.4)	1.5 (34.1)	1.7 (30.6)	1.7 (35.3)	1.5 (16.9)	1.9 (23.1)
		Cohort 1 50 mg	Cohort 2 100 mg*	Cohort 3 200 mg*	Cohort 4 100 mg*	Cohort 5 200 mg*	Cohort 6 300 mg																
Rac(AUC_{tau})	2.4 (37.5)	2.7 (18.6)	3.3 (26.9)	3.3 (27.2)	2.7 (30.5)	3.6 (15.8)																	
Rac(C_{max})	1.3 (33.4)	1.5 (34.1)	1.7 (30.6)	1.7 (35.3)	1.5 (16.9)	1.9 (23.1)																	
<p>*Subjects in Cohorts 2 & 4/Cohorts 3 & 5 received different doses sublingual buprenorphine in stabilization period</p> <ul style="list-style-type: none"> For norbuprenorphine, the accumulation ratios ranged between 1.0 to 1.7 and 0.2 to 1.0, respectively, for AUC_{tau} and C_{max} across the dose range, which suggests little/no apparent accumulation of norbuprenorphine. 																							
Metabolites	<ul style="list-style-type: none"> Buprenorphine is metabolized to its major metabolite, norbuprenorphine, primarily by CYP3A4 & to a lesser extent by CYP2C8 In vitro studies have shown some pharmacological activity associated with norbuprenorphine, however, norbuprenorphine steady-state plasma concentrations in humans after SC administration are very low (AUC Norbuprenorphine/Buprenorphine ratio is 0.20). 																						
Absorption	Absolute/Relative Bioavailability	The absolute bioavailability of SC buprenorphine has not been determined in human, however, the mean (%CV) absolute bioavailability of SC buprenorphine in the dog was reported as 64% (22). (Reference: RBRS-C031-60-09)																					
	Tmax	Median (range) for buprenorphine = 24 h (4-36 h) Median (range) for norbuprenorphine = 12 h (6-48 h)																					
Distribution	Vd/F or Vd	Once absorbed, buprenorphine distributes extensively into body, as evidenced by large mean apparent Vd/F of 1.61X1000 L (8.5%).																					
	% bound	Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.																					
Elimination	Route	A mass balance study of sublingual buprenorphine 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																					

		<p>unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).</p> <p>[Reference: SUBOXONE® 2015]</p>																			
	Terminal t _{1/2}	The apparent terminal plasma half-life for buprenorphine ranged between 1078 to 1573 hours (45 to 66 days) following single SC doses.																			
	CL/F or CL	In a single ascending dose study, the apparent clearance (CL/F) remained fairly constant over the dose range (approximately 66 L/h)																			
Intrinsic Factors	Age	TBD; will be evaluated in population PK analysis of Phase 3 data																			
	Sex	TBD; will be evaluated in population PK analysis of Phase 3 data																			
	Race	TBD; will be evaluated in population PK analysis of Phase 3 data if feasible																			
	Hepatic Impairment	<p>The effect of hepatic impairment on the pharmacokinetics of SC buprenorphine has not been evaluated in a dedicated Phase I study, however, it has been evaluated after sublingual administration. The systemic exposure to buprenorphine is about 2-fold higher in subjects with moderate and severe hepatic impairment after sublingual administration of buprenorphine.</p> <table border="1" data-bbox="815 1356 1435 1776"> <thead> <tr> <th colspan="4">Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine following SUBOXONE administration (change relative to healthy subjects)</th> </tr> <tr> <th>PK Parameter</th> <th>Mild Hepatic Impairment (Child-Pugh Class A) (n=9)</th> <th>Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)</th> <th>Severe Hepatic Impairment (Child-Pugh Class C) (n=8)</th> </tr> </thead> <tbody> <tr> <td colspan="4" style="text-align: center;">Buprenorphine</td> </tr> <tr> <td>C_{max}</td> <td>1.2-fold increase</td> <td>1.1-fold Increase</td> <td>1.7-fold increase</td> </tr> <tr> <td>AUC_{last}</td> <td>Similar to control</td> <td>1.6-fold increase</td> <td>2.8-fold increase</td> </tr> </tbody> </table> <p>[Reference: SUBOXONE® 2015]</p>	Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine following SUBOXONE administration (change relative to healthy subjects)				PK Parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)	Buprenorphine				C _{max}	1.2-fold increase	1.1-fold Increase	1.7-fold increase	AUC _{last}	Similar to control	1.6-fold increase
Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine following SUBOXONE administration (change relative to healthy subjects)																					
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C _{max}	1.2-fold increase	1.1-fold Increase	1.7-fold increase																		
AUC _{last}	Similar to control	1.6-fold increase	2.8-fold increase																		

		The impact of hepatic impairment on buprenorphine exposure after SC administration will be further evaluated as part of the population PK analysis of Phase 3 data.
	Renal Impairment	The effect of renal impairment on the pharmacokinetics of SC buprenorphine has not been evaluated in a dedicated Phase I study. Systemic clearance of buprenorphine would not be expected to be related to renal function, as buprenorphine clearance is considered to occur mainly by hepatic extraction and metabolism. Less than 1 % is excreted as unchanged buprenorphine after sublingual administration. Creatinine clearance will be investigated as a covariate in the population pharmacokinetic modeling of Phase 3 clinical study data.
Extrinsic Factors	Drug interactions/ CYP3A4 inhibitors	<p>The effects of CYP3A4 inhibitors on buprenorphine exposure in subjects treated with SC buprenorphine have not been evaluated in a dedicated Phase 1 study, however, the interaction between ketoconazole and sublingual/transdermal administration of buprenorphine has been evaluated.</p> <p>Co-administration of ketoconazole with sublingual buprenorphine resulted into two-fold increase in mean buprenorphine C_{max} and AUC. The increase in exposure could be due to inhibition of first-pass metabolism because a fraction of the sublingually administered drug is swallowed and absorbed through the gut.</p> <p>When transdermal buprenorphine was co-administered with ketoconazole, no clinically significant interaction was observed (Kapil 2012). As another parenteral route, it is expected that subcutaneous (SC) administration will also by-pass the first-pass metabolism in the liver and intestine. Therefore, it is not expected that a clinically meaningful drug-drug interaction between SC buprenorphine and CYP3A4 inhibitors will occur.</p>

	Drug interactions/ CYP3A4 inducers	CYP3A4 inducers may induce the metabolism of buprenorphine and, therefore, may cause an increase in the clearance of the drug potentially leading to a decrease in buprenorphine plasma concentrations. It is not known whether the effects of CYP3A4 inducers are dependent on the route of administration of buprenorphine.
	Food Effects	<ul style="list-style-type: none"> Not applicable for subcutaneous formulation
Expected High Clinical Exposure Scenario	<p>The geometric mean C_{max} at steady state was 9.38 ng/mL after 300 mg monthly SC buprenorphine administration. Although a 2-fold increase in systemic exposure has been observed in patients with severe hepatic impairment after sublingual administration, use of subcutaneous buprenorphine will not be recommended in this population. It is also expected that no clinically meaningful drug-drug interaction between SC buprenorphine and CYP3A4 inhibitors will occur as summarized above. Two published studies (Umbricht et al., 2004; Huestis et al., 2013) have reported very high levels (137.7 ng/mL) of buprenorphine after single doses of buprenorphine administered IV at doses up to 16 mg in non-treatment seeking opioid users.</p>	
Preclinical Cardiac Safety	<p>The effects of buprenorphine alone or in combination with naloxone on the cardiovascular system was evaluated and are consistent with the known pharmacology of buprenorphine and other opioid drugs. No cardiac safety studies were conducted with SC buprenorphine, however, due to the well-known pharmacology of buprenorphine no unpredicted adverse reactions are anticipated. No changes in electrocardiography were seen in a 9-month repeat dose dog study with SC buprenorphine when measured pre-dose and immediately following the 9th dose.</p> <p>IN VITRO</p> <p>Buprenorphine is reported to inhibit the <i>Ik</i> human ether-a-go-go-related gene (<i>hERG</i>), with a 50% inhibitory concentration (IC_{50}) value of 7.5 μM and an estimated plasma peak drug concentration (C_{max}) of 36 nM, yielding an IC_{50}/C_{max} ratio of 208. When compared with IC_{50} values of 9.8 μM (IC_{50}/C_{max} ratio = 2.7) for methadone (Katchman 2002), buprenorphine has significantly higher safety margin (77 times) for the IC_{50}/C_{max} ratio. The clinical plasma mean C_{max} at the recommended human dose of 300 mg is about 9.38 ng/mL or about 0.019 μM. These data correspond to a large safety margin of 395-times higher than the <i>hERG</i> IC_{50} from clinical exposure levels.</p> <p>IN VIVO</p> <p>No significant effects on cardiovascular parameters or electrocardiogram (ECG) were seen in repeated-dose studies with buprenorphine/naloxone (1:1 or 3:2) in dogs, although one study found a dose-related trend toward slightly increased heart rate and an increase in mean arterial pressure at intramuscular doses > 8-times the recommended human dose of 300 mg on a mg/m² basis. Moreover, in the 9-month repeat dose study with SC buprenorphine, there were</p>	

	<p>no observed changes in electrocardiography. The NOAEL was the high-dose of 40 mg/kg, which corresponds a mean C_{max} values on Day 225 of 101.3 ng/ml. These data correspond to a safety margin of 11-times higher than the clinical plasma mean C_{max} of 9.38 ng/ml for the recommended human dose of 300 mg.</p>
<p>Clinical Cardiac Safety</p>	<p>The Clinical Cardiac Safety summary is based on a total of 5 completed clinical studies and <u>preliminary</u> results from the Phase 3 Double Blind study as below:</p> <p>Single-dose FTIH study (RB-US-10-0011): This FTIH study was designed to evaluate the safety and tolerability of a single SC injection of RBP-6000 containing 20 mg buprenorphine, to characterise its PK profile in 12 opioid-dependent subjects. 5 of the 12 subjects who received RBP-6000 experienced a TEAE of elevated blood pressure (details unknown but rated as mild in intensity). Of these 5 subjects, 2 had a medical history of elevated systolic blood pressure prior to entering of study. In the other 3 subjects, the elevated blood pressure returned to normal without any changes to study medication. No respiratory depression, temperature elevations, clinically significant lowered oxygen saturation or ECG abnormalities were observed for those events. There were no TEAEs with QT prolongation or other ECG associated parameter. No discontinuations due to or other cardiac adverse events were reported. There were no patterns or trends in clinical laboratory findings, vital sign measurements, ECG results or physical examination findings. (Source: RB-US-10-0011 CSR)</p> <p>Single Ascending Dose (SAD) study (RB-US-11-0020): The SAD study was designed to assess the safety, tolerability and PK profile of single SC injections of RBP-6000 containing 50 mg, 100 mg or 200 mg buprenorphine. A total of 48 subjects received RBP-6000. 8 SAEs were reported in 7 subjects of which chest pain was reported in 2 subjects and aortic dissection in 1 subject (details below):</p> <p>A 57-year-old white male, received 50 mg RBP-6000 on (b) (6) and chest pain began about 50 hours post dose. The subject had a history of intermittent, non-cardiac chest pain that began in (b) (6) and was ongoing at the time of the study. The subject complained of sharp parasternal pain that worsened with inspiration and was considered of moderate severity. SpO₂ and vital signs were within normal limits so the subject was admitted to the hospital to rule out a cardiac origin of the chest pain. The chest pain was determined to be not related to treatment with RBP-6000, all associated symptoms completely resolved on (b) (6) and did not result in removal of the RBP-6000 depot.</p> <p>Another 46-year-old white male receiving 200mg of RBP-6000 experienced chest pain and nonspecific thoughts of suicide. The subject had a history of intermittent non cardiac chest pain and hypertension since 2 years and was ongoing at the time of the study. The chest pain was considered of moderate severity and was determined to be not related to treatment with RBP-6000.</p>

A 58-year-old white male, experienced an Acute Type A aortic dissection on (b) (6), 17 weeks after receiving 50 mg RBP-6000 on (b) (6). The subject had a history of drug use, tobacco use, and dyslipidemia that were all ongoing during the time of the study. The subject reported to the emergency room with chest pain on (b) (6) after using cocaine. The subject was admitted to the hospital and diagnosed with an Acute Type A aortic dissection and underwent surgery to replace the ascending aorta on (b) (6). Following surgery, the subject experienced atrial fibrillation and chest pain, both of which were not considered SAEs and were well controlled with medication provided after the surgery. The subject was discharged from the hospital on (b) (6) at which point the aortic dissection was considered resolved and did not result in removal of the RBP-6000 depot. The aortic dissection was assessed as being of moderate severity and was determined to be not related to treatment with RBP-6000.

There were no other TEAEs with QT prolongation, other ECG associated parameter or other cardiac adverse events reported. There were no patterns or trends in clinical laboratory findings, vital sign measurements, ECG results or physical examination findings. (Source: RB-US-11-0020 CSR)

Multiple Ascending Dose study (RB-US-12-0005): A total of 89 opioid-dependent, treatment-seeking subjects received RBP-6000. A total of 6 subjects (6.7%) experienced a TEAE of tachycardia of which 2 subjects were in cohort 6 (300mg), 2 in cohort 5 (200mg) and 1 subject each in cohort 2 (100mg) and 3(200mg) of which 3 were considered as not related to study medication. A total of 5 subjects (5.6%) experienced a TEAE of Sinus tachycardia in cohort 4 (3 subjects) and cohort 5 (2 subjects) of which 4 were not related to study medication. 2 subjects (2.2%) reported a TEAE of blood pressure increased in cohort 1 (50mg) and cohort 5 (200mg) both considered as non-related to study medication. 1 subject (1.1%) reported a TEAE of atrioventricular block first degree in cohort 3 (200mg), mild in severity and related to study medication. No Serious cardiac adverse events were reported. There were no pattern or trends in clinical laboratory findings, vital sign measurements, ECG results or physical examination findings. (Source: Listing 16.2.7 RB-US-12-0005)

An opioid blockade study (RB-US-13-0002): A total of 39 subjects (opioid-dependent, not treatment-seeking) were randomised and subsequently received RBP-6000 containing 300 mg of buprenorphine. 3 (7.7%) subjects reported a TEAE of tachycardia considered not related to RBP-6000, 1 subject (2.6%) reported blood pressure increased, 1 subject (2.6%) reported hypertension and 3 subjects (7.7%) reported hypotension. None of these subjects had clinically significant changes from baseline, no TEAEs were reported with associated QT prolongation or other ECG associated parameter. A TEAE of non-cardiac chest pain was reported in 1 (2.6%) subject which was assessed as not related to RBP-6000. No serious cardiac adverse events were reported. There were no patterns or trends in clinical laboratory findings, vital sign measurements, ECG results or physical examination findings. (Source: RB-US-13-0002 CSR)

Single-dose Molecular-Weight study (RB-US-13-0006): In this study a total of 47 opioid-dependent treatment-seeking subjects were dose-stabilized on SUBOXONE Sublingual film prior to administration of a single SC injection of RBP-6000 containing 300 mg buprenorphine. No serious or non-serious cardiac adverse events or discontinuations due to cardiac adverse events were reported. There were no TEAEs with QT prolongation or other ECG associated parameter reported. There were no patterns or trends in clinical laboratory findings, vital sign measurements, ECG results or physical examination findings. (Source: RB-US-13-0006 CSR).

Preliminary Results Phase 3 Double Blind study (RB-US13-0001-Analysis Ongoing): Out of 505 subjects randomized, 504 subjects were treated and 1 subject was randomized in error, therefore did not receive the dose of study medication. Subjects were randomized to RBP-6000 300 mg every 28 days subcutaneously, or 300 mg x 2 injections followed by 100 mg RBP-6000 injections for the remainder of the study, or to placebo containing injections. The number of subjects randomized to various treatment groups were as follows: N=201 in 300/300 group, N=203 in 300/100 group and N=100 in the placebo group.

Five (0.9%) subjects experienced TEAE's of QTc prolongation. 1 subject (b) (6) had a QTc prolongation which was considered as related to study drug, however this subject was using Asthalin inhaler for his concurrent condition of Asthma and had an underlying medical history of hypertension since (b) (6) which was ongoing at the time of this event. This subject was then asymptomatic and clinically stable. The following table indicates the dose assignment and characteristics of the TEAE related to QTc.

Subject	AE Term	Severity	Relatedness	SAE	Treatment group
(b) (6)	QTc Prolongation	Moderate	Related	No	300 mg treatment group
(b) (6)	QTc Prolongation	Mild	Not related	No	300 mg treatment group
(b) (6)	QTc Prolongation	Mild	Not related	No	300 mg treatment group
(b) (6)	QTc Prolongation	Mild	Not related	No	100 mg treatment group
(b) (6)	QTc Prolongation	Mild	Not related	No	100 mg treatment group

The table below represents preliminary data for the shift of QTcF from the baseline for the above subjects with QTc prolongation.

SUBJID	AGE	SEX	VISIT	VISIT N	ECG	Finding	Baseline	Change from Baseline
(b) (6)	33	M	DAY 71	14	QTcF (msec)	476	423	53
(b) (6)	32	F	DAY 71	14	QTcF (msec)	498	428	70
(b) (6)	40	M	Last Visit	99	QTcF (msec)	488	419	69
(b) (6)	39	F	DAY 148	28	QTcF (msec)	480	431	49
(b) (6)	55	M	DAY 155	29	QTcF (msec)	462	440	22

4 subjects reported a TEAE of tachycardia of which 2 TEAE were of moderate intensity and 2 TEAEs were of mild intensity. There were 2 TEAE's of increased blood pressure, 3 TEAE's of heart rate increased which were all mild in intensity. None of these events were considered related to RBP-6000. 1 TEAE of supraventricular tachycardia and supraventricular extra-systole was reported. None were severe in intensity and considered as not related to RBP-6000.

1 SAE of Acute myocardial infarction occurred in a 52-year-old male subject. He received RBP-6000 (the first 2 doses contained buprenorphine 300 mg followed by 4 doses of 100 mg). Relevant medical history included hypertension, hypercholesterolemia, and upper respiratory infection. Concomitant medications included metoprolol for hypertension, cephalexin for infection and gabapentin for sciatic pain. This event was considered severe in intensity, recovered and assessed as not related to RBP-6000.

Conclusion: 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.

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/s/

GOPICHAND GOTTIPATI
11/09/2017

LARS JOHANNESSEN
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MOHAMMAD A RAHMAN
11/09/2017

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11/09/2017

CHRISTINE E GARNETT
11/09/2017

Clinical Inspection Summary

Date	October 30, 2017
From	Damon Green, M.D., M.S., Reviewer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Swati Patwardhan, Regulatory Project Manager Emily Deng, M.D., Clinical Reviewer Celia Winchell, M.D., Clinical Team Leader Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
NDA #	209819
Applicant	Indivior, Inc.
Drug	Sublocade (Buprenorphine-ATRIGEL)
NME	No
Therapeutic Classification	Opioid analgesic-partial agonist/antagonist
Proposed Indication	Treatment of moderate to severe opioid use disorder
Consultation Request Date	July 7, 2017
Summary Goal Date	October 30, 2017
Action Goal Date	November 30, 2017
PDUFA Date	November 30, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Hassman, Mofsen, Rutrick, and Kelsh were inspected in support of this NDA. The sponsor and CRO, Indivior Inc. and (b) (4) respectively, were also inspected. The final classification of the inspections of Drs. Hassman and Mofsen was No Action Indicated (NAI). The preliminary classification of the inspections of Drs. Rutrick and Kelsh was NAI. The preliminary classification of the inspection of Indivior Inc. was Voluntary Action Indicated (VAI). The preliminary classification of the inspection of (b) (4) was NAI.

Based on the results of these inspections, 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.

II. BACKGROUND

The Applicant submitted this NDA to support the use of Sublocade (Buprenorphine-ATRIGEL) subcutaneously injected depot for the treatment of moderate to severe opioid use disorder (OUD).

Inspections were requested of the following protocols in support of this application:

Protocol RB-US-13-0001 entitled, “A Randomized, Double-blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy, Safety, and Tolerability of Multiple Subcutaneous Injections of Depot Buprenorphine (RBP-6000 [100 mg and 300 mg]) Over 24 Weeks in Treatment-Seeking Subjects With Opioid Use Disorder.”

This study took place at 36 sites within the United States, beginning 01/28/2015 and ending 04/29/2016. A total of 505 subjects were enrolled.

The primary objective of this study was to assess the efficacy of RBP-6000 compared with placebo in the treatment of opioid use disorder. 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 collected from Week 5 through Week 24.

RB-US-13-0002 entitled, “A Multiple-Dose Study of Blockade of Subjective Opioid Effects, Plasma Levels, and Safety of Subcutaneous Injections of Depot Buprenorphine (RBP-6000) in Subjects With Opioid Use Disorder.”

This study took place at one site in Kansas starting on 11/19/2013 and ending 7/29/2014. A total of 39 subjects were enrolled.

The primary objective was to demonstrate that the “Drug Liking” visual analog scale (VAS) measured after challenge with 6 mg and 18 mg of hydromorphone was non-inferior to the “Drug Liking” VAS measured after challenge with placebo at Weeks 1-4 post first injection of buprenorphine 300 mg (RBP-6000). The primary efficacy endpoint was opioid blockade through the first 4 weeks following administration of RBP-6000 as measured by visual analog scale (VAS) assessment of “Drug Liking”.

Rationale for Site Selection

Dr. David Hassman had the highest enrollment in the study while Dr. Daniel Rutrick had the second highest enrollment.

The single site study conducted by Dr. Debra Kelsh was selected for inspection because the data from the study was considered critical for approval.

The sponsor and CRO inspections were requested to assess, across sites, what quality measures were or were not in place to assure data integrity.

III. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects Enrolled	Inspection Dates	Classification
Site #9 David Hassman, MD 175 Cross Keys Road Centennial Center Building 300-B Berlin, NJ 8009	RB-US-13-0001 Subjects: 48	18-27 Sept 2017	NAI
Site #16 Ricky Mofsen, MD 10330 Old Olive Road St. Louis, MO 63141	RB-US-13-0001 Subjects: 25	18-21 Sept 2017	NAI
Site #28 Daniel Rutrick, MD 521 Mount Auburn Street Suite 107 Watertown, MA 02472	RB-US-13-0001 Subjects: 45	5-11 Sept 2017	NAI*
Debra Kelsh, MD Vince & Associates Clinical Research, Inc. 10103 Metcalf Avenue Overland Park, KS 66212	RB-US-13-0002 Subjects: 39	3-6 Oct 2017	NAI*
Sponsor Indivior Inc. 10710 Midlothian Turnpike STE 430 Richmond, Virginia 23112	RB-US-13-0001 RB-US-13-0002	10-19 Oct 2017	VAI*
CRO (b) (4)	RB-US-13-0001	(b) (4)	NAI*

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations; Data unreliable.

*Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. David Hassman, M.D.

For Protocol RB-US-13-0001, 89 subjects were screened and 48 subjects were enrolled, with 28 completing the study.

Records reviewed included informed consents, IRB approvals, FDA Form 1572, drug accountability, source documentation for urine testing and ECGs, Medical Outcomes Study Short Form - 32 (SF-36v), Healthcare Resource Utilization (HCRU) Questionnaire, Columbia Suicide Severity Rating Scale (C-SSRS), Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), Opioid Craving VAS (Visual Analog Scale), Timeline Follow Back Interview (TLFB), Clinical Global Impression - Severity Scale (CGI-S), Clinical Global Impression - Improvement Scale (CGI-I), Medication Satisfaction Questionnaire (MSQ), EuroQuoL-5 Dimensions-5 Levels (EQ-5D-5L), Injection Site Grading Scale (ISGS), blinded Urine Drug Screen (UDS) laboratory test results, eCRFs (with audit trails), protocol deviations, adverse events, inclusion/ exclusion criteria, screen failures, and concomitant medications.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events. Informed consent was obtained properly for each of the subjects.

A Form FDA 483 was not issued at the conclusion of the inspection.

2. Ricky Mofsen, M.D.

For Protocol RB-US-13-0001, 129 subjects were screened and 25 subjects were enrolled, with 13 completing the study.

Records reviewed included SOWS and COWS scores, subject self-reporting of illicit drug use electronic data, IRB correspondence, study staff training, sponsor monitoring activities (including site monitoring visits and sponsor monitor communication and training), investigator financial disclosure, subject source documents, eCRFs, informed consents, protocol deviations, adverse events and serious adverse events, and drug accountability.

Primary efficacy endpoint data were verifiable (the blinded urine drug screen data was not available at the site but was verified during the sponsor inspection). There was no evidence of underreporting of adverse events. Informed consent was obtained properly for each of the enrolled subjects.

A Form FDA 483 was not issued at the conclusion of the inspection.

3. Daniel Rutrick, M.D.

Primary efficacy endpoint data were verifiable, though these data were not available during the inspection of this site. Rather, the blinded urine drug screen data were verified during the sponsor inspection. In addition, the self-reported illicit opioid use data were obtained from the sponsor through an information request and subsequently verified by this OSI reviewer. During review of the self-reported data, a discrepancy was noted for subject (b) (6) in that for weeks 16, 17, 18, and 20, the source document indicated negative illicit opioid use, while the submitted line listings indicated positive illicit opioid use. The impact of this discrepancy on the results of the study, if any, would be to disadvantage the study drug.

A potential conflict of interest was noted by the inspector in that Dr. Rutrick, who was blinded for this study, is the father of the CEO of this site, who was unblinded for IMP accountability purposes. No rules appear to have been broken. The DAAAP clinical review team were made aware of this issue, and a sensitivity analysis was performed that excluded this site's data. The efficacy results were similar.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Debra Kelsh, M.D.

For Protocol RB-US-13-0002, 342 subjects were screened and 39 subjects were enrolled, with 30 completing the study.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events. Informed consent was obtained properly for each of the subjects.

A Form FDA 483 was not issued at the conclusion of the inspection.

5. Indivior Inc. (Sponsor)

Most of the regulatory obligations for Protocol RB-US-13-0001 had been transferred to the CRO, (b) (4). The field investigator found that the sponsor generally upheld the responsibilities that they did not transfer except for monitoring oversight.

An FDA Form 483, Inspectional Observations, was issued at the conclusion of the inspection because the sponsor failed to ensure proper monitoring of the study. Specifically, for Protocol RB-US-13-0001, the Indivior Study Operations Manager did not carry out several monitoring oversight functions as required in the unblinded oversight monitoring plan. As a result, inadequate drug accountability at several sites was missed until after study closeout.

Notwithstanding these observations, the studies appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

6. (b) (4) (CRO)

No significant issues were found with (b) (4) oversight of Protocol RB-US-13-0001. A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data handled by this CRO and submitted by the sponsor may be used in support of the respective indication.

{See appended electronic signature page}

Damon Green, M.D., M.S.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

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cc:

Central Doc. Rm.
DAAAP /Division Director/Hertz
DAAAP/Medical Team Leader/Winchell
DAAAP /Project Manager/ Patwardhan
DAAAP/Medical Officer/Deng
OSI/Office Director/Burrow
OSI/DCCE/ Division Director/Khin
OSI/DCCE/Branch Chief/Ayalew
OSI/DCCE/Team Leader/Kronstein
OSI/DCCE/GCPAB Reviewer/Green
OSI/ GCP Program Analysts/Patague
OSI/Database PM/Dana Walters

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/s/

DAMON C GREEN
10/30/2017

PHILLIP D KRONSTEIN
10/30/2017

KASSA AYALEW
10/30/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: October 12, 2017
Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number: NDA 209819
Product Name and Strength: Sublocade (buprenorphine) injection, 100 mg and 300 mg
Product Type: Single ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Indivior, Inc.
Submission Date: May 30, 2017
OSE RCM #: 2017-1067
DMEPA Safety Evaluator: Millie Shah, PharmD, BCPS
DMEPA Team Leader: Otto L. Townsend, PharmD

1 REASON FOR REVIEW

This review provides our evaluation of the proposed labels and labeling for Sublocade (buprenorphine) injection from a medication error perspective. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested this review as part of their evaluation of the 505(b)(2) NDA submission for Sublocade.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed labels and labeling and prescribing information for Sublocade to identify deficiencies that may lead to medication errors and to identify other areas that can be improved.

The proposed product is supplied in a carton containing one pouch with a sterile pre-filled syringe of Sublocade injection in the Atrigel delivery system, one oxygen absorber, and one sterile 19-gauge $\frac{5}{8}$ inch safety needle. Sublocade is intended to be administered to patients by healthcare professionals.

Pre-filled Syringe Label, Pouch Labeling, and Carton Labeling

Our review of the labels and labeling identified that the established name is not presented with the dosage form. Thus, we recommend the Applicant revise the presentation of the established name so that it is presented with the approved dosage form as determined by the Office of Pharmaceutical Quality (OPQ).

We note the labels and labeling of the 300 mg strength use a (b) (4) scheme. The proprietary name is presented in a (b) (4) scheme for both the 100 mg and 300 mg strengths. The use of the same (b) (4) font for the proprietary name and one of the product's strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors. Thus, we recommend the Applicant revise the font color of the proprietary name or revise the color scheme of the 300 mg strength, so that either the strength or the proprietary name appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.

We identified the package type term (b) (4) on the labels and labeling, including the Prescribing Information (PI). We notified the OPQ reviewer and defer to OPQ to determine the correct package type term for this product and convey this to the Applicant.

Sublocade should be stored under refrigeration at 2 - 8°C (35.6 - 46.4°F). Once outside the refrigerator this product may be stored in its original packaging at room temperature, 15 – 30°C (59 – 86°F), for up to 7 days prior to administration. We recommend the Applicant add the statement, “Discard after ___/___/___” on the carton labeling so that healthcare professionals have a space to write the discard date once the product is removed from refrigeration.

We identified negative statements ((b) (4) on the pouch and carton labeling that may be misinterpreted because the word “(b) (4)” may be overlooked. Thus, we recommend revising the negative statements to use affirmative language (“Attach the needle at the time of administration” and “Use only the needle provided”).

We identified that the linear drug bar code is missing from the labels and labeling. Thus, we recommend that the Applicant add the linear bar code as it is often used as an additional verification before drug dispensing and administration.

We determined that the C-III symbol competes in prominence with the proprietary and established names on the pre-filled syringe label. Thus, we recommend the Applicant decrease the size of the C-III symbol on the pre-filled syringe label so that it does not compete in prominence with the proprietary or established names. Additionally, we note the C-III symbol appears immediately following the established name. Thus, we recommend the Applicant relocate the C-III symbol away from the established name so that it does not compete in prominence.

The statement, “To be administered by a healthcare provider only” is located on the back panel of the carton labeling. We recommend relocating this statement to the principal display panel and increasing its prominence to minimize the risk of anyone other than a healthcare professional administering the product.

Instructions for Use (IFU)

To illustrate how to use the product, labeled figures are included; however, they are not referenced within the instructional text. We recommend that the figures be referred to in the text of the steps as appropriate to increase clarity.

In Step 7, we recommend relocating the statement, “TRADENAME is for subcutaneous injection only. Do not inject intravenously or intramuscularly” as the first statement under this step to increase the prominence of this important information.

Prescribing Information (PI)

We note that the Dosage and Administration section in the Highlights of Prescribing Information does not include the statement, “See Full Prescribing Information for administration instructions.” We are concerned that healthcare professionals may overlook important administration instructions if they refer to the Highlights of Prescribing Information only. Thus, we recommend adding this statement to the Highlights of Prescribing Information to alert healthcare providers of the administration instructions in the Full PI and to minimize the risk for administration errors.

We recommend adding information about the color and other identifying characteristics of Sublocade as determined by OPQ to the How Supplied section. We recommend revising the storage statement to state, “Store under refrigeration at 2 - 8°C (35.6 - 46.4°F).” to increase clarity. Additionally, we recommend relocating the statement, “Discard TRADENAME if left at room temperature for longer than 7 days.” immediately after the statement, “Once outside the refrigerator this product may be stored in its original packaging at room temperature, 15 – 30°C (59 – 86°F), for up to 7 days prior to administration.” to minimize the risk of healthcare professionals overlooking the discard instructions.

We identified the abbreviation “G” in the Dosage Forms and Strengths section of both the Highlights of Prescribing and Full Prescribing Information. We recommend replacing the abbreviation with the full, intended meaning, “gauge” to minimize the risk for confusion.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed labels and labeling that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

If you have further questions or need clarifications, please contact Davis Mathew, OSE Project Manager, at 240-402-4559.

4.1 RECOMMENDATIONS FOR THE DIVISION

We revised the *Dosage and Administration* and *How Supplied* sections of the Highlights of Prescribing Information and Full Prescribing Information and provided a detailed summary below for review and consideration by DAAAP.

A. Highlights of Prescribing

1. We recommend adding the statement, “See Full Prescribing Information for administration instructions” to the *Dosage and Administration* section to alert healthcare providers of the administration instructions in the Full PI and to minimize the risk for administration errors.
2. We recommend replacing the abbreviation, “G,” in the *Dosage Forms and Strengths* section with the full, intended meaning, “gauge” to minimize the risk for confusion.

B. Full Prescribing Information

1. We identified the package type term (b) (4) in the *How Supplied* section. We defer to the Office of Pharmaceutical Quality (OPQ) to make the final determination of the correct package type term for this product. Ensure that the OPQ-determined package type is consistent throughout labels and labeling and is conveyed to the Applicant.
2. We recommend adding information about the color and other identifying characteristics of Sublocade as determined by OPQ to the *How Supplied* section.
3. We recommend revising the storage statement in the *How Supplied* section to state, “Store under refrigeration at 2 - 8°C (35.6 - 46.4°F).” to increase clarity. Additionally, we recommend relocating the statement, “Discard TRADENAME if left at room temperature for longer than 7 days.” immediately after the statement, “Once outside the refrigerator this product may be stored in its original packaging at room temperature, 15 – 30°C (59 – 86°F), for up to 7 days prior to administration.” to minimize the risk of healthcare professionals overlooking the discard instructions.
4. In Section 2.5 *Method of Administration*, we recommend that the figures be referred to in the text of the IFU steps as appropriate to increase clarity.
5. In Section 2.5 *Method of Administration*, Step 7 we recommend relocating the statement, “TRADENAME is for subcutaneous injection only. Do not inject intravenously or intramuscularly” as the first statement under this step to increase the prominence of this important information.
6. See A.2

4.2 RECOMMENDATIONS FOR INDIVIOR, INC.

We recommend the Applicant implement the following prior to approval of this NDA:

A. Pre-filled Syringe Label

1. Revise the presentation of the established name so that it is presented with the approved dosage form as determined by the Office of Pharmaceutical Quality (OPQ).^a
2. The 300 mg strength uses a (b) (4) scheme. The proprietary name is presented in a (b) (4) scheme for both the 100 mg and 300 mg strengths. The use of the same (b) (4) font for the proprietary name and one of the product’s strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors. Thus, revise the font color of the proprietary name or revise the color scheme of the 300 mg strength, so that either the strength or the proprietary

^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

name appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.^b

3. The linear drug bar code is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible. Therefore, add a linear bar code to each individual pre-filled syringe label as required per 21CFR 201.25(c)(2). Additionally, ensure the linear bar code is surrounded by enough white space to allow scanners to read the bar code properly in accordance with 21 CFR 201.25(c)(1)(i). Furthermore, note that linear bar codes placed in a horizontal position may not scan due to curvature of the container.^c
4. Decrease the size of the C-III symbol and relocate it away from the established name so that it does not compete in prominence with the proprietary or established names.

B. Pouch Labeling

1. See A.1, A.2, and A.3
2. Add the statement, “Discard SUBLOCADE if left at room temperature for longer than 7 days” in bold font immediately after the statement, “Once outside the refrigerator, this product may be stored in its original packaging at room temperature, 15°–30°C (59°–86°F), for up to 7 days prior to administration” to increase clarity and prominence of the storage information.
3. Revise the negative statements (b) (4) to use affirmative language (“Attach the needle at the time of administration” and “Use only the needle provided”) because the word (b) (4) may be overlooked, which may lead to the statements being misinterpreted.^d
4. Relocate the C-III symbol away from the established name so that it does not compete in prominence.

C. Carton Labeling

1. See A.1, A.2, and A.3
2. See B.3 and B.6
3. Use bold font for the statement “Discard SUBLOCADE if left at room temperature for longer than 7 days” and relocate the statement immediately after the statement, “Once outside the refrigerator, this product may be stored in its original packaging

^b Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

^c Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79

^d Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

at room temperature, 15°–30°C (59°–86°F), for up to 7 days prior to administration” to increase clarity and prominence of the storage information.

4. We recommend adding the statement, “Discard after ___/___/___” following the storage information so that healthcare professionals can write the discard date once the product is removed from refrigeration.
5. Relocate the statement, “To be administered by a healthcare provider only” from the back panel to the principal display panel and increase the prominence of this statement by use of different colors, boxing, or some other means to minimize the risk of anyone other than a healthcare professional administering the product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Sublocade that Indivior, Inc. submitted on May 30, 2017, and the listed drug (LD).

Table 2. Relevant Product Information for Sublocade and the Listed Drug		
Product Name	Sublocade	Subutex
Initial Approval Date	Not Applicable	October 8, 2002
Active Ingredient	Buprenorphine	Buprenorphine hydrochloride
Indication	treatment of moderate-to-severe opioid use disorder in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product.	Treatment of opioid dependence
Route of Administration	Subcutaneous	sublingual
Dosage Form	Injection	tablet
Strength	100 mg; 300 mg	2 mg; 8 mg
Dose and Frequency	300 mg monthly. The dose may be decreased to 100 mg based upon tolerability	12 mg to 16 mg once daily
How Supplied/ Container Closure	Prefilled syringe with safety needle	White HDPE bottles with 30 tablets per bottle
Storage	Store at 2 - 8°C (35.6 - 46.4°F). Once outside the refrigerator this product may be stored in its original packaging at room temperature, 15 – 30°C (59 – 86°F), for up to 7 days prior to administration.	Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 1, 2017, we searched the L:drive and AIMS using the term, Sublocade to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews relevant to the current label and labeling review.

APPENDIX C. N/A

APPENDIX D. N/A

APPENDIX E. N/A

APPENDIX F. N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^e along with postmarket medication error data, we reviewed the following Sublocade labels and labeling submitted by Indivior, Inc. on May 30, 2017.

- Prefilled syringe label
- Container label
- Carton labeling
- Prescribing Information, including Instructions for Use (Image not shown)

G.2 Label and Labeling Images



^e Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MILLIE C BRAHMBHATT
10/12/2017

OTTO L TOWNSEND
10/13/2017