

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209819Orig1s000

CLINICAL REVIEW(S)

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Application Type	NDA
Application Number(s)	209819
Priority or Standard	Priority Review
Submit Date(s)	05/30/2017
Received Date(s)	05/30/2017
PDUFA Goal Date	11/30/2017
Division/Office	DAAAP/OND II
Reviewer Name(s)	Fang Emily Deng, MD., MPH., MS
Review Completion Date	11/06/2017
Established Name	Buprenorphine extended-release injection
(Proposed) Trade Name	Sublocade (RBP-6000)
Applicant	Indivior INC
Formulation(s)	Buprenorphine extended-release injection
Dosing Regimen	300 mg/month x 2 doses followed by 100 mg/month, with option to increase to 300 mg/month
Applicant Proposed Indication(s)/Population(s)	Treatment of moderate to severe opioid use disorder (OUD) in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of moderate to severe opioid use disorder (OUD) in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product, and had dose-stabilization for a minimum of 7 days

Table of Contents

Glossary.....	8
1. Executive Summary	10
1.1. Product Introduction.....	10
1.2. Conclusions on the Substantial Evidence of Effectiveness	11
1.3. Benefit-Risk Assessment	12
1.4. Patient Experience Data.....	19
2. Therapeutic Context	20
2.1 . Analysis of Condition.....	20
2.1. Analysis of Current Treatment Options	21
3. Regulatory Background	23
3.1. U.S. Regulatory Actions and Marketing History.....	23
3.2. Summary of Presubmission/Submission Regulatory Activity	23
3.3. Foreign Regulatory Actions and Marketing History.....	26
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	26
4.1. Office of Scientific Investigations (OSI)	26
4.2. Product Quality	27
4.3. Clinical Microbiology	27
4.4. Nonclinical Pharmacology/Toxicology	27
4.5. Clinical Pharmacology	28
Pharmacokinetic of Phase 3 dosing regimens	30
4.6. Devices and Companion Diagnostic Issues	31
4.7. Consumer Study Reviews	31
5. Sources of Clinical Data and Review Strategy	31
5.1. Table of Clinical Studies.....	31
5.2. Review Strategy.....	35
6. Review of Relevant Individual Trials Used to Support Efficacy	35
6.1. Phase 3, double-blind, placebo-controlled, efficacy and safety trial (13-0001).....	35
CDER Clinical Review Template	2
<i>Version date: September 6, 2017 for all NDAs and BLAs</i>	

6.1.1. Study Design.....	35
6.1.2. Study Results.....	62
6.2. Opioid blockade study (RB-US-13-0002).....	75
7. Integrated Review of Effectiveness.....	78
7.1. Assessment of Efficacy Across Trials.....	78
8. Review of Safety.....	81
8.1. Safety Review Approach.....	82
8.2. Review of the Safety Database.....	83
8.2.1. Overall Exposure.....	83
8.2.2. Relevant characteristics of the safety population:.....	85
8.2.3. Adequacy of the safety database:.....	93
8.3. Adequacy of Applicant’s Clinical Safety Assessments.....	93
8.3.1. Issues Regarding Data Integrity and Submission Quality.....	93
8.3.2. Categorization of Adverse Events.....	93
8.3.3. Routine Clinical Tests.....	95
8.4. Safety Results.....	95
8.4.1. Deaths.....	95
8.4.2. Serious Adverse Events.....	95
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects.....	103
8.4.4. Significant Adverse Events.....	107
8.4.5. Treatment Emergent Adverse Events and Adverse Reactions.....	109
8.4.6. Laboratory Findings.....	112
8.4.7. Vital Signs.....	114
8.4.8. Electrocardiograms (ECGs).....	114
8.4.9. QT.....	114
8.4.10. Immunogenicity.....	116
8.5. Analysis of Submission-Specific Safety Issues.....	116
8.5.1. Injection site reactions.....	116
8.5.2. Hepatic effects.....	119
8.5.3. CNS depression.....	122

8.5.4. Opioid Withdrawal Signs and Symptoms.....	124
8.5.5. Reparatory depression.....	126
8.5.6. Orthostatic hypotension	126
8.5.7. Acute pancreatitis	128
8.5.8. Cardiac disorder	129
8.6. Safety Analyses by Demographic Subgroups	132
8.7. Specific Safety Studies/Clinical Trials	133
8.8. Additional Safety Explorations	133
8.8.1. Human Carcinogenicity or Tumor Development	133
8.8.2. Human Reproduction and Pregnancy.....	133
8.8.3. Pediatrics and Assessment of Effects on Growth	133
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound	133
8.9. Safety in the Postmarket Setting.....	134
8.9.1. Safety Concerns Identified Through Postmarket Experience.....	134
8.9.2. Expectations on Safety in the Postmarket Setting	134
8.9.3. Additional Safety Issues From Other Disciplines	135
8.10. Integrated Assessment of Safety	135
9. Advisory Committee Meeting and Other External Consultations.....	135
10. Labeling Recommendations	137
10.1. Prescription Drug Labeling	137
6.1 Clinical Trials Experience.....	138
10.2. Nonprescription Drug Labeling.....	140
11. Risk Evaluation and Mitigation Strategies (REMS)	141
12. Postmarketing Requirements and Commitments.....	143
13. Appendices	144
13.1. References	144
13.2. Financial Disclosure	144

Table of Tables

Table 1: Composition of RBP-6000 300 mg and 100 mg	11
Table 2: Currently available treatments for opioid use disorder or opioid dependence.....	22
Table 3: Key recommendations conveyed & Applicant’s response.....	24
Table 4 Single-dose RBP-6000 300 mg pharmacokinetic parameters.....	29
Table 5: PK parameters comparison between “run-in” Subutex 24 mg daily dose and RBP-6000 300 mg	30
Table 6: PK Parameters after 6 Injections for 300/100 mg and 300/300 mg Dosing Regimens Calculated from Model-Based Individual PK Predictions in the Ph3DB Study (Applicant’s table)	31
Table 7: Listing of Clinical Trials Relevant to this NDA 209819	33
Table 8: Composition of RBP-6000 placebo (100 mg and 300 mg)	36
Table 9: Schedule of Events: Screening and SUBOXONE Sublingual Film Induction	43
Table 10: Schedule of Events: RBP-6000 Injection Visits 1–3.....	48
Table 11: Schedule of Events: RBP-6000 Injection Visits 4–6, End of Study/Early Termination Visit and Follow-up	52
Table 12: Urine Drug Screen immunoassays (Applicant’s table).....	57
Table 13: Urine Drug screen confirmatory testing information (Applicant’s table)	58
Table 14: Derivation of the composite primary efficacy endpoints	61
Table 15 Subject Disposition All Screened Subjects (Study 13-0001)	63
Table 16: Distribution of protocol violation.....	64
Table 17: Protocol violation due to UDS missing.....	65
Table 18: Demographic characteristics of the study population (13-0001).....	65
Table 19: Baseline drug use history distribution (13-0001).....	66
Table 20: Cumulative percentage of negative opioid use from week 5-24.....	68
Table 21: UDS results vs TLFB week 5 to week 24 (Excluding site 20)	71
Table 22: Safety database for RBP-6000.....	82
Table 23: Injections received by treatment group in Phase 3 studies	84
Table 24: Cumulative treatment exposure by weeks in Phase 3 studies	85
Table 25: Cumulative exposure by dose level in Phase 3 studies.....	85
Table 26: Baseline demographic for Phase 3 DB study (13-0001).....	86
Table 27: Baseline demographic for Phase 3 OL, long-term study (13-0003)	88
Table 28: Baseline medical history distribution in Phase 3 studies.....	91
Table 29: Baseline BMI group distribution in Phase 3 studies	92
Table 30 : TEAE definitions for all clinical studies (Applicant’s table)	93
Table 31: SAE summary for Phase 1 and 2 studies	99
Table 32: SAEs summary for Phase 3 studies	100
Table 33: SAEs summary for thromboembolic disorders	102
Table 34: TEAEs leading to drug discontinuation in Phase 3 studies	104
Table 35: TEAEs leading to drug dose reductions in Phase 3 OL, long term study (13-0003)....	106

Table 36: Severe TEAEs summary in Phase 3 study (13-0001) (Percentage occurrence \geq 2%)..	108
Table 37: Severe TEAEs summary in Phase 3 OL study (13-0003) (Percentage occurrence \geq 2%)	
.....	108
Table 38: Common adverse events in Phase 3 DB study (13-0001) (\geq 2%)	109
Table 39: Common adverse events in Phase 3 OL study (13-0003) (\geq 2 %)	110
Table 40: Subjects with LFT values greater than upper limit of normal in Phase 3 DB study (13-0001)	113
Table 41: : Subjects with LFT values greater than upper limit of normal in Phase 3 open-label study (13-0003).....	113
Table 42: TEAEs related to injection site reactions by severity in Phase 3 studies	117
Table 43: TEAEs related to injection site reactions by actions on study drugs	118
Table 44: Reported TEAEs related to hepatic injuries by action on study treatment in Phase 3 studies	120
Table 45: Reported TEAEs related to hepatic injuries by severity in Phase 3 studies.....	121
Table 46: TEAEs related to CNS depression in Phase 3 studies	123
Table 47: TEAEs related to opioid withdrawal signs and symptoms in Phase 3 studies (Applicant’s table)	125
Table 48: TEAEs related to orthostatic hypotension in Phase 3 studies (Applicant’s table)	127
Table 49: TEAEs related to acute pancreatitis in Phase 3 studies	129
Table 50: TEAEs related to cardiac disorder in Phase 3 studies	131
Table 51: Adverse Events Event Occurrence & Proportion Report for Sex Reporting Events with at least Overall 2% Occurrence in Phase 3 DB study (13-0001)	132
Table 52: Adverse Drug Reactions for Phase 3 Double-Blind Study: \geq 2% of Subjects Receiving RBP-6000.....	138
Table 53: Injection site adverse drug reactions reported \geq 2 subjects in the Phase 3 studies (Adapted from Applicant’s table)	140
Table 54: Clinical investigators list in the financial disclosure certification form	145

Table of Figures

Figure 1: The proposed anatomical injection sites	11
Figure 2: Mean Plasma Concentrations of Buprenorphine after a single dose of RBP-6000 300 mg	29
Figure 3: Pivotal safety and efficacy study (13-0001) scheme	38
Figure 4: Cumulative distribution function of percentage negative use	69
Figure 5: Urine Opioid screen results for individual subjects	70
Figure 6: CDF of the percentage abstinence for subjects by tapering status	71
Figure 7: Key secondary efficacy endpoints: percentage of subjects meeting criteria for responder or treatment success	72
Figure 8: Relationship Between the Proportion of Subjects with Negative Opioid Use and Buprenorphine Plasma Concentration (Study 13-0001)	73
Figure 9: CDF of percentage abstinence for injection drug users	74
Figure 10: CDF of percentage abstinence for non-injection drug users	74
Figure 11: Mean Difference of Emax (in Unipolar Scales) between Hydromorphone and Placebo over Weeks (Non-inferiority margin I=20) (Generated by CSS statistic reviewer)	76
Figure 12: Placebo-Corrected Drug-Liking By Time and Hydromorphone Dose Level	77
Figure 13: Placebo-Corrected Drug-Liking vs. Associated Buprenorphine Concentration (Response to 18 mg Hydromorphone Challenge)	78
Figure 14: Buprenorphine plasma profile for subject (b) (6)	96
Figure 15: QT effects of RBP-6000 (Generated by QT-IRT team)	115

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Sublocade (RBP-6000) is a drug-device combination product with 18% (weight/weight) buprenorphine base in the ATRIGEL Delivery System in a prefilled syringe. Buprenorphine, the active ingredient in RBP-6000, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine was approved for medical use in the United States in 1981. The ATRIGEL Delivery System is a non-aqueous solution consisting of a biodegradable polymer, 50:50 poly(DL-lactide-co-glycolide) with a carboxylic acid end group (PLGH) and a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). The ATRIGEL Delivery System has been used in other FDA approved products such as ELIGARD, which is indicated for the palliative treatment of advanced cancer. RBP-6000 provides sustained plasma levels of buprenorphine over a minimum of 28 days and is proposed for the treatment of moderate to severe opioid use disorder (OUD) in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. The product should be used as part of a complete treatment plan to include counselling and psychosocial support. The proposed dosing regimens include 300 mg monthly for the first 2 months followed by maintenance treatment of 100 mg or 300 mg monthly based on the clinical condition of the patient. Sublocade (RBP-6000) has a number of novel features. If approved, it would be the first once-monthly injectable buprenorphine product indicated for the treatment of opioid use disorder. Secondly, it would be the first buprenorphine product designed to achieve a target plasma concentration that is predicted to be sufficient to occupy more than 70% of mu-opioid receptors. The Applicant hypothesizes that this threshold ensures blockade of exogenous opioids, which is believed to be important in effectively treating OUD¹².

Sublocade (RBP-6000) is designed to be subcutaneously injected in the abdominal area once monthly. Sublocade (RBP-6000) will be provided with two dosage strengths of 300 mg and 100 mg in a prefilled syringe with a 19 G 5/8-inch needle. Table 1 summarizes the composition and approximate delivered volume for each dosage strength. The entire contents of the prefilled syringe will be administered with each dose. The approximate volume delivered is 0.5 mL for the 100 mg injection and 1.5 mL for the 300 mg injection. Injections will be rotated sequentially

¹Greenwald, M. K., Comer, S. D., & Fiellin, D. A. (2014). Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. *Drug and alcohol dependence*, 144, 1-11.

² Greenwald, M. K., Johanson, C. E., Moody, D. E., Woods, J. H., Kilbourn, M. R., Koeppe, R. A., ... & Zubieta, J. K. (2003). Effects of Buprenorphine Maintenance Dose on [mu]-Opioid Receptor Availability, Plasma Concentrations, and Antagonist Blockade in Heroin-Dependent Volunteers. *Neuropsychopharmacology*, 28(11), 2000-11

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

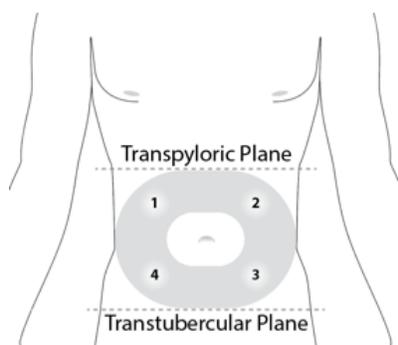
at labeled four spots on the abdomen region between the transpyloric and transtubercular planes. (Figure 1)

Table 1: Composition of RBP-6000 300 mg and 100 mg

Raw Materials in RBP-6000	100 mg Dosage	300 mg Dosage
Buprenorphine	100 mg	300 mg
Poly(DL-lactide-co-glycolide)	178 mg	533 mg
N-methyl-2-pyrrolidone	278 mg	833 mg
Approximate Delivered Volume	0.5 mL	1.5 mL

Source: The Applicant’s drafted labeling

Figure 1: The proposed anatomical injection sites



Source: The Applicant’s drafted labeling

1.2. Conclusions on the Substantial Evidence of Effectiveness

Indivior, the Applicant, has provided efficacy data from a multiple center, double-blind, placebo-controlled, 24-week efficacy and safety study in combination with an inpatient opioid blockade study. The inpatient opioid blockade study identified that 300 mg of Sublocade achieved a target plasma concentration greater than 2 ng/ml after the first subcutaneous injection and provided effective blockade of opioid effects, using hydromorphone challenge tests. This study provides confirmatory evidence of efficacy. Dosing regimens of RBP-6000 300/300 mg (6 doses of 300 mg SC injections) and RBP-6000 300/100 mg (2 doses of 300 mg SC injections followed by 4 doses of 100 mg SC injections) were tested in the pivotal study. The efficacy of Sublocade (RBP-6000) for both dose regimens (300/300 mg and 300/100 mg) has been demonstrated in both primary endpoint and key secondary endpoint analyses. A total of 504 treatment seeking patients with moderate to severe opioid use disorder as defined by DSM-5 diagnosis were randomized to receive Sublocade (RBP-6000) or placebo SC injection for 24 weeks under double-blind conditions after 2 weeks open-label induction and a dose adjustment phase with Suboxone film. The primary endpoint, defined as the cumulative

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

distribution function of the percentage negative drug assessments³ from Week 5 through 24, was statistically significantly superior in the Sublocade treatment group to that in the placebo group. Approximately 12-13% of patients in each active treatment group had achieved 100% negative drug use over the 20-week efficacy ascertainment period. The key secondary endpoint was the proportion of subjects achieving treatment success (responder), which was defined as any subject with $\geq 80\%$ of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 5 and Week 24. The treatment success rate was statistically significantly higher in the Sublocade treatment group (28 %-29 %) compared with the placebo group (2%).

1.3. **Benefit-Risk Assessment**

³ In the protocol, this is called “percentage abstinence,” but as implemented, it refers to the percent of weeks in which the weekly drug use assessments (urine toxicology and self-report) were negative. “Abstinence,” *per se*, was not required.

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

Benefit-Risk Integrated Assessment

Sublocade (RBP-6000) is the first once-monthly injectable buprenorphine product that has been developed to treat moderate to severe opioid use disorder (OUD) in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product, and had dose-stabilization for a minimum of 7 days. The product should be used as part of a complete treatment plan to include counselling and psychosocial support. The product is intended to be administered by health care providers in healthcare settings. This reviewer recommends approval on the basis of the efficacy and safety information currently available.

OUD, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is a chronic, relapsing disease characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and physical consequences. OUD is associated with a higher rate of morbidity and mortality compared with the general population. Opioid dependence as defined by DSM-IV and earlier editions is comparable with OUD (moderate to severe subtype) as defined by DSM-5 criteria. Similarly, opioid abuse is comparable with the mild subtype of OUD. Three million, eight-hundred thousand people in the United States aged 12 and older reported past month misuse of a prescription pain medication in 2015⁴, Among them, 2 million had a DSM-IV substance use disorder diagnosis for opioids, during the past year. OUD is a common cause of drug overdose and accidental injuries in young adults in the USA. Medication assisted therapies of OUD (MAT) are effective treatment of OUD and reduce morbidity and mortality in patients with OUD. Most of current MAT options (buprenorphine with/without naloxone, methadone, oral naltrexone) are daily use products. Limitations of daily use products include poor medical compliance and fluctuating buprenorphine plasma levels throughout the day. Daily use MAT products with mu-agonist or partial agonist properties are subject to diversion, misuse, abuse and accidental pediatric exposure. Overall, treatment of OUD is an unmet public health need.

The efficacy of Sublocade (RBP-6000) is demonstrated by the Phase 3, 24 weeks, double-blind, placebo-controlled, pivotal study (13-0001), comparing Sublocade (RBP-6000) 300/300 mg, 300/100 mg, and placebo on the percentage of negative drug use between Week 5 and Week 24. Primary efficacy endpoint analysis indicates that the cumulative distribution function of the percentage weekly UDS negative for opioids and self-reports negative for illicit opioid use from week 5 through 24 were statistically significantly superior in both the RBP-6000 300/300 mg group and the RBP-6000 300/100 mg groups. About 12-13% of patients in each active treatment group had achieved 100% negative drug use assessments over the 20-week efficacy ascertainment period. Both the RBP-6000 300/300 mg and the RBP-6000 300/100 mg groups showed

4

2015 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Administration, Rockville, MD 2016.

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

a significant increase in responder rate or treatment success rate by approximately 20% compared with the placebo group. The efficacy of Sublocade (RBP-6000) is further supported by a Phase 2, inpatient, opioid blockade study (13-0002). The opioid blockade study (13-0002) identified that 300 mg of Sublocade achieved a target plasma concentration greater than 2 ng/ml after the first subcutaneous injection and provided effective blockade of opioid effects, using hydromorphone challenge tests. This study provides confirmatory evidence of efficacy.

The safety profile of Sublocade (RBP-6000) is well-characterized, based on safety data collected from 848 subjects who received RBP-6000 300/300 mg or RBP-6000 300/100 mg or RBP-6000 300/Flex SC injection in the Phase 3 double-blind, efficacy and safety study and the Phase 3 open-label, long-term safety study. Based on this profile, the major toxicities of concern with Sublocade (RBP-6000) are liver toxicity, CNS effects, and GI effects which are expected systemic buprenorphine effects, as well as formulation specific injection site reactions. The overall safety experience of RBP-6000 is consistent with the safety profile of transmucosal buprenorphine products. The local injection tolerability is acceptable as most of injection site reactions were mild to moderate. Dose dependent effects were observed in the Phase 3 controlled study (13-0001) as there was a higher percentage of subjects with TEAEs related to injection site reactions, elevated liver enzymes and early drop outs due to TEAEs in the RBP-6000 300/300 mg group compared with the RBP-6000 300/100 mg group. The most common TEAEs leading to drug discontinuation or drug dose reduction in the RBP-6000 groups included elevated liver enzymes, injection site reactions, sedation, constipation, somnolence, and lethargy.

Sublocade (RBP-6000) is the first, extended-released, monthly injectable, buprenorphine product developed for the treatment of OUD. RBP-6000 has many benefits compared with the existing transmucosal buprenorphine products. First of all, it delivers a plasma concentration predicted to be sufficient to occupy more than 70% of mu-opioid receptors and has been shown to block exogenous opioids and effectively treats OUD. Secondly, RBP-6000 improves medication compliance, reduces the risk of pediatric accidental exposure and, when administered as intended by a health care provider, reduces misuse and abuse via IV or other routes. Both dosing regimens (RBP-6000 300/300 mg and 300/100 mg) were equally effective. The safety profile of both dosing regimens is acceptable, given the severity of this disease in the current context of the opioid epidemic in the USA and the demonstrated benefits. The identified safety concerns, such as liver toxicity and injection site reactions can be addressed through appropriate product labeling. Given the dose dependent hepatic effects and dose dependent injection site reactions for RBP-6000, the recommended dosing regimens for RBP-6000 are two initial doses of 300 mg monthly followed by 100 mg maintenance doses monthly. Increasing the maintenance dose to 300 mg is optional only for patients for which the benefits outweigh the risk, as judged by clinicians. Sublocade (RBP-6000) appears to provide advantages over other available therapies and represents a new option for patients with OUD.

While some of the risks of RBP-6000 are similar to those of the approved transmucosal buprenorphine products, this formulation, which is supplied in a pre-filled syringe, may present specific safety issues. If patients obtain direct access to the product, there is a risk they may choose to attempt to inject the product intravenously. Notably, the consequences of intravenous injection of the contents of the pre-filled syringe are not known. However, based on in vitro evaluation, it is anticipated that there is a risk of occlusion, local tissue damage, and emboli. Therefore, the product should be administered by a health care provider in a clinical setting and an appropriate REMS would be needed to prevent the product from being in the hands of the patient prior to administration.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • OUD is a chronic relapsing disease with higher mortality and morbidity compared with the general population • Common comorbidities of OUD include psychiatric disorders, injection drug use, infections, hepatitis A, B, C and HIV, polysubstance abuse, etc • OUD is associated with the increased risk of drug overdose and accidental trauma • OUD is associated with poor quality of life and is a social economic burden for individuals, families and society 	<ul style="list-style-type: none"> • OUD is a chronic relapsing disease with variable natural history and can be life long • OUD is a common cause of drug overdose in young adults • For patient with OUD, an effective maintenance treatment needs to be established to prevent relapse • MAT decreases mortality and morbidity • Treatment of OUD is an unmet public health need
Current Treatment Options	<ul style="list-style-type: none"> • Current treatment options include non-drug (behavioral) treatment, as well as medication-assisted treatment (MAT) with antagonists (naltrexone), agonists (methadone) or partial agonists (buprenorphine) • Most of current MAT options (buprenorphine with/without naloxone , methadone, oral naltrexone) are daily use products 	<p>Buprenorphine monthly depot injection would be a desirable addition to the therapeutic armamentarium:</p> <ul style="list-style-type: none"> • Convenience of monthly vs daily dosing • Provides consistent buprenorphine levels above 2 ng/ml at steady state

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> • Limitations of daily use products include poor medical compliance and fluctuating buprenorphine plasma levels throughout the day • Daily use mu-agonist and partial agonist MAT products are subject to diversion, misuse, abuse and accidental pediatric exposure • Subdermal implant (PROBUPHINE) is a modified release formulation for a 6 month administration only for patients clinically stable on low-moderate dose of transmucosal buprenorphine (≤ 8 mg buprenorphine). Surgical implant insertion and removals for Probuphine are burdensome for primary care physicians and patients • Depot naltrexone (VIVITROL) cannot be initiated until patients are fully detoxified, and may not be suitable or acceptable for all patients 	<ul style="list-style-type: none"> • Improves medical compliance • Reduces diversion, misuse, abuse and accidental pediatric exposure • No surgical procedure needed • No rescue buprenorphine needed
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> • The pivotal double-blind, placebo-controlled, efficacy trial (13-0001) (N=504) evaluated RBP-6000 dosing regimens 300/ 300 mg and 300/100 mg compared to placebo for percentage of negative drug use between treatment Week 5 and Week 24 • 13 % of patients in RBP-6000 300/300 mg group and 12% of patients in the RBP-6000 300/100 mg group achieved 100 % negative drug use, while only 1 % of patients in the placebo group achieved 100 % negative drug use over the 20-week efficacy ascertainment period • The study quality is adequate and the study population is an adequate representation of the treatment population with OUD in the USA • The primary efficacy endpoint is the clinically relevant surrogate endpoint used previously by the division as a basis for approval of Vivitrol • RBP-6000 is administered subcutaneously every month under 	<p>Both RBP-6000 dosing regimens 300/ 300 mg and 300/100 mg are equally effective to treat patients with moderate to severe OUD</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	supervision and provides advantages over daily dose MAT products	
Risk and Risk Management	<ul style="list-style-type: none"> • Buprenorphine, the active ingredient of RBP-6000, has been approved since 2002 for the treatment of opioid dependence. The systemic buprenorphine effects of RBP-6000 are consistent with the established safety profiles of transmucosal buprenorphine products • Systemic effects of buprenorphine associated with RBP-6000 ($\geq 2\%$ occurrence) include headache, nausea, constipation, vomiting, elevated liver enzymes, sedation and somnolence • Common injection site reactions included injection site pain, pruritus and erythema • Treatment-emergent adverse events leading to drug discontinuation were reported in $\leq 5\%$ of subjects in all treatment groups • TEAEs leading drug dose reductions were reported in 7.3% of subjects receiving RBP-6000 in Phase 3 OL study • No Hy's law case was identified in the clinical development program • No SAEs related to injection site reactions • One death occurred in the RBP-6000 300/300 mg group due to homicide gunshot • A total of 50 non-fatal SAEs occurred among 42 subjects in the Phase 3 studies and the majority of SAEs were not drug related • The incidence rate of TEAEs leading to drug discontinuation was slightly higher in the RBP-6000 300/300 mg group (5%) than the RBP-6000 300/100 mg group (3.5%) 	<ul style="list-style-type: none"> • The size of the safety database for RBP-6000 was adequate to characterize safety profile • The overall safety experience is consistent with the safety profile of transmucosal buprenorphine products indicated for the treatment of OUD • The local injection tolerability is acceptable • The safety database did not identify major new safety issues compared to the established safety profile of transmucosal buprenorphine, despite higher plasma exposures • Identified safety concerns, including liver toxicity and injection site reactions, can be addressed by appropriate labeling • Agency proposes REMS to mitigate potential adverse consequences due to intravenous self-administration by ensuring that RBP-6000 is only dispensed and administered in healthcare settings by HCPs

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> • The incidence rate of injection site reactions was higher in the RBP-6000 300/300 mg group 18.9 % than in the RBP 300/100 mg group (13.8%) • The incidence rate of ALT \geq 3x ULN (post-baseline) was higher in the RBP-6000 300/300 mg group (12.4 %) than in the RBP-6000 300/100 mg group (5.4%) • The incidence rate of AST \geq 3x ULN (post-baseline) was higher in the RBP-6000 300/300 mg group (11.4%) than in the RBP-6000 300/100 mg group (7.9%) • RBP-6000 is intended to be administered by health care providers in health care settings. If patients obtain direct access to the product, there is a risk they may attempt to inject the product intravenously. resulting in a risk of occlusion, tissue damage, and emboli 	<ul style="list-style-type: none"> • Agency proposes a one-time certification of healthcare settings that order and dispense the product: Certification is to include an agreement to put systems into place that prevent RBP-6000 from being dispensed directly to the patient

1.4. Patient Experience Data

Patient and clinician-reported data were included as secondary and exploratory endpoints.

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	<input type="checkbox"/> Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	<input type="checkbox"/> Patient reported outcome (PRO)	CGI-S, SF-36 v2 ⁵ VAS, SOWS
	<input type="checkbox"/> Observer reported outcome (ObsRO)	
	<input type="checkbox"/> Clinician reported outcome (ClinRO)	COWS
	<input type="checkbox"/> Performance outcome (PerfO)	
	<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Natural history studies	
	<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
	<input type="checkbox"/> Other: (Please specify)	
	<input type="checkbox"/> Patient experience data that were not submitted in the application, but were considered in this review:	
	<input type="checkbox"/> Input informed from participation in meetings with patient stakeholders	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Other: (Please specify)	
	Patient experience data was not submitted as part of this application.	

⁵ CGI-S I: clinical global impression-severity. SF-36v2: 36-item short form health survey

2. Therapeutic Context

2.1 . Analysis of Condition

OUD, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is a chronic, relapsing disease characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and physical consequences. OUD is associated with a higher rate of morbidity and mortality compared with the general population. Opioid dependence as defined by DSM-IV and earlier editions is comparable with OUD (moderate to severe subtype) as defined by DSM-5 criteria. Opioid abuse is similar to the mild subtype of OUD. In 2015, about three million, eight-hundred thousand people in the United States aged 12 and older reported past month misuse of a prescription pain medication. Among them, 2 million had a DSM-IV substance use disorder diagnosis on opioids during the past year⁶.

DSM-5 diagnostic criteria⁷:

- Opioids are often taken in larger amounts or over a longer period than was intended
- A persistent desire or unsuccessful efforts to cut down or control opioid use
- A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects
- Craving, or a strong desire or urge to use opioids
- Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home
- Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids
- Important social, occupational, or recreational activities are given up or reduced because of opioid use
- Recurrent opioid use in situations in which it is physically hazardous
- Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
- Tolerance
- Withdrawal

⁶ 2015 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Administration, Rockville, MD 2016.

⁷ https://www.uptodate.com/contents/opioid-use-disorder-epidemiology-pharmacology-clinical-manifestations-course-screening-assessment-and-diagnosis?source=search_result&search=opioid%20use%20disorder&selectedTitle=1~150

The severity of OUD can be specified as a subtype based on the number of criteria present:

- Mild – Two to three criteria
- Moderate – Four to five criteria
- Severe – Six or more criteria

2.1. Analysis of Current Treatment Options

Buprenorphine a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence. A sublingual film formulation was approved in 2010. Two other transmucosal formulations have subsequently been approved. Additionally, an implantable buprenorphine product delivering a low to moderate dose of buprenorphine was approved in 2015 for stable patients for whom the dose is adequate. Approximately 12.2 million prescriptions from outpatient retail pharmacies were dispensed and approximately 1.6 million patients received a dispensed prescription for buprenorphine tablets or films during 2016. Primary care physicians accounted for 39% of prescriptions, followed by psychiatrists (21%), osteopaths (14%), emergency physicians (4%) and anesthesiologists (4%).

Buprenorphine was developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the μ -receptor. Like methadone, buprenorphine's activity at the μ -receptor was expected to relieve patients' urge to use illicit opioids, and like methadone, the long duration of action would allow patients to achieve a steady state with daily dosing, without the alternating highs and lows associated with opioid abuse that impair daily functioning. At sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, deterring abuse of these substances for buprenorphine-maintained patients. However, compared to methadone, buprenorphine is less likely to cause life-threatening respiratory depression and was therefore expected to be more suitable for take-home use.

Due to its partial agonist properties, the euphorogenic effects of buprenorphine are understood to reach a "ceiling" at moderate doses, beyond which increasing doses of the drug do not produce the increased effect that would result from full opioid agonists. This was expected to limit its attractiveness as a drug of abuse, an additional feature permitting take-home use.

In addition, when a partial agonist displaces a full agonist at the receptor, the relative reduction in receptor activation can produce withdrawal effects. Individuals dependent on full agonists may therefore experience sudden and severe symptoms of withdrawal if they use buprenorphine. This was predicted to serve as a further deterrent to abuse.

Unfortunately, despite these features, buprenorphine sublingual products have been

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

As shown in Table 2, FDA approved products for the treatment of opioid dependence include buprenorphine oral transmucosal formulations; buprenorphine implant; methadone and levomethadyl acetate (LAAM, no longer marketed), both of which are full agonist treatments; and naltrexone (oral and depot formulations), an opioid antagonist. Treatment of addiction with methadone is limited to closely-regulated Opioid Treatment Programs (OTP), which may limit access to treatment. Buprenorphine treatment may be prescribed by specially-qualified health care providers in office practice settings.

Table 2: Currently available treatments for opioid use disorder or opioid dependence

Currently available treatments for opioid use disorder or opioid dependence			
Daily Products			
Generic/Chemical Name	Trade Name	Sponsor	Dosage form(s)
Buprenorphine/ naloxone	Suboxone tablet (generics only)	Indivior	Sublingual tablet
	Suboxone film (also generics)	Indivior	Sublingual film
	Bunavail (also generics)	Biodelivery Sci Intl	Buccal film
	Zubsolv (also generics)	Orexo AB	Sublingual tablet
Buprenorphine	Subutex (generics only)	Indivior	Sublingual tablet
Methadone HCl	Methadose (also generics)	Mallinckrodt	Oral solution Bulk powder Tablet Dispersible tab
Methadone HCl	Dolophine (also generics)	Roxane	Tablet Oral concentrate Oral solution
Naltrexone HCl	ReVia (also generics)	Duramed	Tablet
Modified release Products			
Naltrexone HCl	Vivitrol	Alkermes	Injectable

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

			suspension
Buprenorphine	Probuphine	Braeburn (Previously Titan)	Implant

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Sublocade (RBP-6000) is being developed for maintenance treatment of moderate and severe OUD as defined by DSM-5 and it is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

Sublocade (RBP-6000) is a combination product supplied with a prefilled syringe containing buprenorphine in the ATRIGEL drug delivery system. Indivior, the Applicant, is seeking a 505 (b) (2) approval by relying on published literature to support the safety assessment of the excipients which form the ATRIGEL delivery system, as well as cross-referencing their own applications for buprenorphine. Presubmission regulatory history and relevant clinical information discussed in the meeting are summarized below:

- Pre-IND meeting (04/27/2010)
 - Allowed for 1 Phase III pivotal study for "stabilized" patient population. For new entrants to treatment patient population, a confirmatory study could be required
 - Thorough QT study should be performed
 - Dosing in special populations (e.g., hepatic or renal impairment) should be addressed in the NDA submission
- Type C meeting (05/14/2013)
 - Literature-based justification is not acceptable for opioid blockade
 - An opioid blockade study should be done to identify the dose of RBP-6000 that blocks exogenous opioids with a target exposure of 3 ng/ml. This dose will be studied in the Phase 3 pivotal study
 - Safety database should be adequate to support chronic use
 - Because Indivior received Orphan designation for buprenorphine to treat OUD in the context of developing Subutex and Suboxone, Pediatric Research Equity Act (PREA) requirements are waived
- EOP II meeting (09/30/2014)
 - Additional information was needed to support the toxicology profile of the excipients NMP and 50:50 PLGH
 - Specific recommendations to Phase 3 clinical trial regarding patient population

- and primary and key secondary endpoints
 - Safety database should include at least 500 patients for 6 months and 100 for 12 months
- Risk Evaluation and Mitigation Strategy (REMS) teleconference (9/28/2016)
 - To justify the need for a REMS, the NDA should include data comparing with the current SUBOXONE Film REMS in terms of safety and the goals and objectives
 - Indivior will need to work with DEA to ensure proposed distribution plans are not in violation of applicable laws
- Pre-NDA meeting (12/14/2016)
 - NDA datasets requirements
 - CRF and narrative summary requirements
 - Data pooling strategy

Table 3 summarizes key recommendations conveyed by Agency and Applicant’s response in their NDA submission. Overall, the safety data and efficacy data submitted by the Applicant are consistent with Agency’s recommendations.

Table 3: Key recommendations conveyed & Applicant’s response

Key points	DAAAP recommendations	NDA submissions
Efficacy requirements	Required one Phase 3 pivotal efficacy study for "stabilized" patient population. Required either two efficacy studies or one efficacy study in combination with an opioid blockade study for the new to entrant patient population	A pivotal Phase 3, 24 weeks, double-blind, placebo-controlled study in combination with an inpatient opioid blockade study
Opioid blockade study	The opioid blockade study should be conducted first and provide data to support the selection of dose for the pivotal Phase 3 study	Consistent with FDA’s recommendations 300 mg of Sublocade provides opioid blockade after the first subcutaneous injection and this dose was subsequently used for the pivotal Phase 3 study
Pivotal Phase 3 study	Target study population is new entrants to buprenorphine treatment	Before randomization, treatment-seeking subjects were induced with Suboxone

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

		film for 3 days initially, followed by dose adjustment for 11 days to achieve a dosage range of 8-24 mg
	Primary efficacy endpoint: 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	Consistent with FDA's recommendations
	Key secondary endpoint: responder rate or treatment success rate, defined as any subject with $\geq 80\%$ of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 5 and Week 24	Consistent with FDA's recommendations
	Efficacy outcome measurements: weekly UDS and self-reported illicit opioid use as recorded by TLFBI interview	Consistent with FDA's recommendations
Safety database	~ 500 subjects exposed to the product at marketed dose for ≥ 6 months ~ 100 subjects exposed to the product at marketed dose for \geq one year	Safety data were collected from Phase 3 DB study (13-0001) and Phase 3 OL study (13-0003) The size of safety database met or exceeded the FDA's recommendations for treatment of chronic disease
REMS	Agency required that the Applicant provide evidence that the product poses a greater risk of accidental exposure which would require a restrictive distribution REMS	The Applicant provided in vitro data demonstrating that the product congeals rapidly in the presence of blood and could pose a risk of occlusion or embolus if injected The Applicant proposed a restricted distribution system to ensure that the

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

		product will be administered by a health care provider
Drug-drug interactions	Drug interaction studies are needed to address drug interactions concerns and address dose adjustments when used in conjunction with CYP3A4 inhibitors and inducers	Data collected within the development program and literature review
QT effects	Thorough QT study should be performed	A comprehensive EKG dataset (over 11,900 ECG observations in over 1100 subjects with OUD) with buprenorphine plasma level were submitted and was deemed adequate for review by CDER QT-IRT team
Dosing in special populations	Dosing in special populations (e.g., hepatic or renal impairment) should be addressed in the NDA submission	Literature review and data collected from the development program
Chronic use	Interdose interval, repeat injection concerns, including injection site rotation and repeat use of injection site	Population PK simulation and modeling study results

Source: Reviewer

3.3. Foreign Regulatory Actions and Marketing History

Sublocade (RBP-6000) is not currently marketed in any foreign counties.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Upon Agency request, the Applicant submitted site-level datasets for the pivotal Phase 3 DB study (13-0001). A total of 36 study sites screened subjects and 33 study sites randomized subjects in Phase 3 DB, pivotal study (13-0001). Site 20 was excluded due to compliance issues

CDER Clinical Review Template

26

Version date: September 6, 2017 for all NDAs and BLAs

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

(Audit in June 2015 and closed on August 2015). OSI reviewers did analysis using site selection tool and recommended Site 9, 16 and 28 to be inspected based on SAE outliers or efficacy outliers. Additionally, the site for the opioid blockade study was selected for inspection. OSI reviewer Dr. Damon Green concluded that the studies appear to have been conducted adequately, and the data generated by these sites and submitted by the Applicant appear to be acceptable in support of the respective indication.

4.2. **Product Quality**

The Chemistry, Manufacturing, and Controls (CMC) reviewer raised the concern that the



To ensure that the product would deliver effective levels of buprenorphine, appropriate acceptance specifications for the starting material and release specifications for the finished product were established and agreed to by the Applicant.

4.3. **Clinical Microbiology**

Clinical microbiology data were reviewed by Microbiology reviewer Dr Jonathan Burgos. No issues were identified.

4.4. **Nonclinical Pharmacology/Toxicology**

Nonclinical pharmacology /toxicology data were reviewed by nonclinical reviewer Dr. Gary Bond and Dr. Jay Chang. They concluded that the following are relevant safety information:

“In the nonclinical toxicology studies, the local tissue effects of RBP-6000 were typical of a foreign body reaction to an injected polymeric material and consisted primarily of erythema, edema, and occasional scabbing. Histologically, local cellular damage and inflammatory infiltrates/granulomas were noted in and around the injection sites consistent with an expected foreign body reaction. The effects are likely due to both the vehicle and the local buprenorphine concentration. Given the slow rate of degradation of the polymeric vehicle, these local reactions are expected to take many months to completely resolve. Rotation of the injection sites should prevent cumulative local tissue toxicity.

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

In the 6-month repeat-dose toxicology study in the rat, RBP-6000 increased the incidence of pancreatic acinar cell apoptosis. The Applicant attributed this to the stress induced by the chronic buprenorphine exposure and the local inflammatory reaction of the depot injection. Evidence of stress in these animals included urine stained fur, aggressive behavior, decreased activity, broken/cracked teeth, reduced body weight (males) and reduced food consumption. Reduced body weights/food intake has also been reported to increase pancreatic acinar cell apoptosis in the literature. “

The Applicant also provided new reproductive toxicology studies involving both the vehicle and the finished product. These studies provided updated information for labeling.

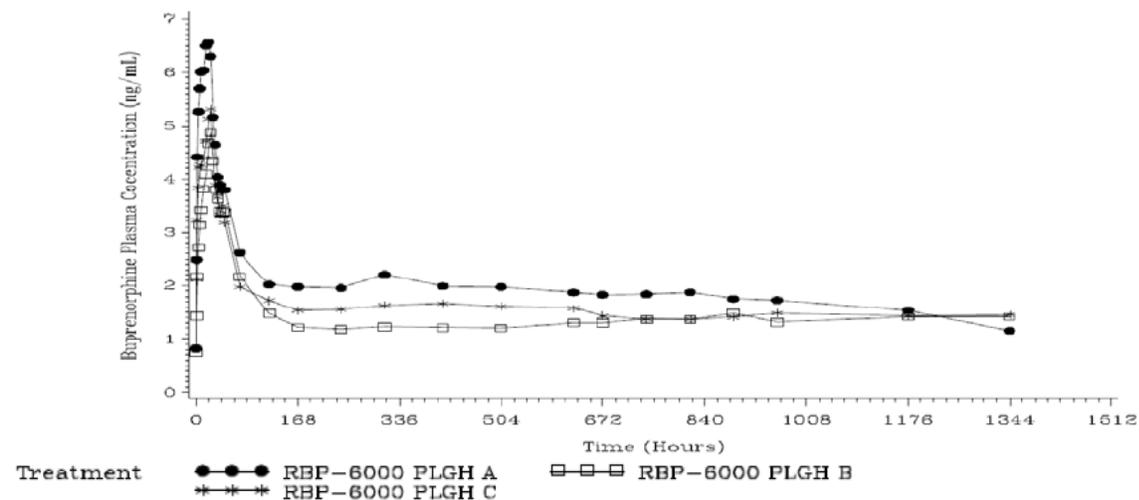
4.5. Clinical Pharmacology

The Clinical Pharmacology reviewers Dr. David Lee / Dr. Yun Xu reviewed the single dose bioavailability studies and multiple dose PK study (12-0005). Dr. Michael Bewernitz reviewed the population PK modeling study. The followings are summary from their reviews:

Single dose bioavailability study (RB-US-11-0020) indicates that C_{max} was observed approximately 24 h post administration after a single dose RBP-6000 100 mg SC injection. Observed buprenorphine levels declined to a plateau until the end of the dosing interval (Day 28), indicating that buprenorphine is slowly released from the RBP-6000 during the dosing interval. After a single-dose RBP-6000 SC injection ranging from 50 to 200 mg, pharmacokinetic parameters increased at a rate that was less than proportional to dose. Per the applicant, following single dose administration, the estimated terminal plasma half-life of buprenorphine ranged between 43 to 60 days.

Study RB-US-11-0006 evaluated the effect of different molecular weights (MW) of the PLGH polymer in the formulation on pharmacokinetics of single dose of 300 mg RBP-6000 after buprenorphine sublingual stabilization or “lead-in” phase in subjects with opioid use disorder. Buprenorphine peak levels were observed approximately 17 h post administration (Figure 2). Buprenorphine pharmacokinetic parameters are presented in Table 4. For the 300 mg dose, the observed mean buprenorphine plasma half-life was 908 h (SD 157 h; note: parameter was represented by only 2 values), corresponding to approximately 38 days. The long half-life is mainly determined by the continuous absorption from RBP-6000 and does not reflect the real elimination half-life of buprenorphine.

Figure 2: Mean Plasma Concentrations of Buprenorphine after a single dose of RBP-6000 300 mg



Treatment ●●● RBP-6000 PLGH A □□□ RBP-6000 PLGH B
 --* RBP-6000 PLGH C

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

Table 4 Single-dose RBP-6000 300 mg pharmacokinetic parameters

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

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

	SD	0.68	0.62	0.47
--	----	------	------	------

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

RBP-6000 PLGH B: RBP-6000 300 mg buprenorphine formulated with 17 kDa PLGH polymer (test treatment), SC injection

RBP-6000 PLGH C: RBP-6000 300 mg buprenorphine formulated with 14 kDa PLGH polymer (reference treatment), SC injection

Hour 312, 504, 672: Table 14.2.2 Summary of plasma concentration of buprenorphine (RBP-6000 phase) Pharmacokinetic set

Source: rbus130006-body.pdf; End-of-Text Table 14 2.6.

Pharmacokinetic of Phase 3 dosing regimens

PK parameters comparison between “Run-in” Subutex daily dose and RBP-6000 was conducted in the Phase 2 MAD study (11-0005). Table 5 compares the PK parameters of RBP-6000 with that of Subutex in subjects who were induced and stabilized with Subutex 24 mg daily dose and then switched to RBP-6000 300 mg injections. Per labeling, 24 mg sublingual buprenorphine is the maximum recommended dose. Most patients get 16 mg sublingual buprenorphine for the maintenance dose. After the first injection, the steady state C_{avg} of RBP-6000 300 mg was comparable with that of Subutex 24 mg daily. After the 4th injection, the steady state C_{avg} of RBP-6000 (4.81 ng/ml) was about 65% higher than that of Subutex 24 mg daily dose. After the 4th injection, the C_{max} of RBP-6000 was comparable with the C_{max} of the Subutex 24 mg daily. The C_{min} of RBP-6000 was higher than that of Subutex 24 mg daily dose.

Table 5: PK parameters comparison between “run-in” Subutex 24 mg daily dose and RBP-6000 300 mg

PK parameters	Subutex 24 mg daily dose (Run-in)	RBP 6000 300 mg (1 st injection)	RBP 6000 300 mg (4 th injection)
Mean $C_{avg ss}$ (ng/ml)	2.907	2.19	4.81*
Mean $C_{max ss}$ (ng/ml)	8.267	5.37	8.22
Mean $C_{min ss}$ (ng/ml)	1.543	1.25	3.35

*Data from cohort of Subutex 12 mg (Run-in) /RBP-6000 300 mg

The Applicant has performed PK modeling- analysis to compare the two dosing regimens that were used in the Phase 3 pivotal efficacy study (13-0001). As shown in Table 6, after the sixth injection, both dosing regimens provide buprenorphine plasma levels of more than 2 ng/ml.

The steady state C_{avg} of the dosing regimen 300/100 mg (3.1 ng/ml) was comparable with that of Subutex 24 mg daily dose (2.907 ng/ml) as shown in Table 5. However, the steady state C_{avg} of the high dose regimen of 300/300 mg (6.3 ng/ml) was two times that of Subutex 24 mg daily

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

dose (2.907 ng/ml). The C_{max} (8.7 ng/ml) of the high dose regimen was comparable with that of Subutex 24 mg daily dose.

The high dosing regimen exposures exceed exposures associated with Subutex, limiting the ability to rely on the safety of Subutex to support the new product. For this reason, the Agency advised the Applicant to provide adequate safety data for this product.

Table 6: PK Parameters after 6 Injections for 300/100 mg and 300/300 mg Dosing Regimens Calculated from Model-Based Individual PK Predictions in the Ph3DB Study (Applicant's table)

Dosing Regimen	Mean C_{avg} (ng/mL)	Mean C_{min} (ng/mL)	Mean C_{max} (ng/mL)
300/100-mg	3.1	2.7	4.1
300/300-mg	6.3	5.1	8.7

4.6. Devices and Companion Diagnostic Issues

Consult reviewer from CDRH team concluded that the NDA 209819 is approvable from the perspective of the applicable Quality System Requirements.

4.7. Consumer Study Reviews

Not applicable for this NDA review.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The Applicant, Indivior, included 7 clinical study reports in this NDA submission as shown in Table 7. These studies included two Phase 3 studies, two Phase 2 studies and three Phase 1 studies.

The Phase 3 pivotal, double-blind, placebo controlled, 24 week, safety and efficacy study (13-0001) in combination with the inpatient opioid blockade study (13-0002) are used to support the efficacy of Sublocade (RBP-6000).

Safety data used for supporting the approval of Sublocade (RBP-6000) included the Phase 3

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

pivotal 24 week safety and efficacy study (13-0001) and the Phase 3 open-label, long-term safety study (13-0003). Safety data from three Phase 1 single dose studies and one Phase 2 multiple dose study were used as supplemental safety data. The opioid blockade study (13-0002) was conducted in a non-treatment-seeking patient population; no SAE was reported and there is no safety data that is relevant to NDA approval from the opioid blockade study.

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 7: Listing of Clinical Trials Relevant to this NDA 209819

Trial Identity	NCT NO	Induction /Dose stabilization Phase	Treatment regimen, mg x doses (number of subjects for safety evaluation)	Treatment Duration/ Follow Up	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>						
Ph3DB 13-0001	NCT02357901	Induction/dose stabilization with Suboxone SL film up to 14 days, titrated up to 8 to 24 mg	RBP-6000 300 x 6 (N=201) RBP-6000 300 x 2+100 x 4 (N=203) Placebo (N=100)	24 weeks (6 SC injections)	Opioid dependent (DSM-5) Treatment seeking	36 sites screened, 33 sites randomized
<i>Studies to Support Safety</i>						
Ph3OL 13-0003	NCT02510014	Induction/dose stabilization with Suboxone SL film up to 14 days, titrated up to 8 to 24 mg	Roll-over : RBP-6000 300 300 x 1 then flex x 5 (N=113) RBP-6000 100 300 x 1 then flex x 5 (N=112) Placebo 300 x 1 then flex x 5 (N=32) De novo RBP-6000 300 x 1 then flex x 11 (N=412)	Roll-over: 24 weeks (6 SC injections) De novo: 48 weeks (12 SC injections)	Opioid dependent (DSM-5) Treatment seeking	39 sites
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>						
Ph2 OB 13-0002	NCT02044094	Induction/dose stabilization with Suboxone SL film up to 14 days, titrated up to 8 to 24 mg	RBP-6000 300 x 2 (N=39)	8 weeks (2 SC injections)	Opioid dependent (DSM-5) Not-Treatment seeking	Single center

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

Ph2MAD 12-0005	NCT01738503	SUBUTEX SL tablet Induction/dose stabilisation: 13 days Cohort 1: 8 mg Cohort 2: 12 mg Cohort 3: 24 mg Cohort 4: 8 mg Cohort 5: 14 mg Cohort 6: 8 to 24 mg	RBP-6000 Cohort 1: 50 x 4 (N=15) Cohort 2: 100 x 4 (N=15) Cohort 3: 200 x 4 (N=15) Cohort 4: 100 x 4 (N=15) Cohort 5: 200 x 4 (N=15) Cohort 6: 300 x 6 (N=14)	Cohorts 1-5: 16 weeks (4 SC injections) Cohort 6: 24 weeks (6 SC injections)	Opioid dependent (DSM-IV-TR) Treatment-seeking	Single center
Phase 1 single dose, PK studies						
SAD: 11-0020	NCT03002961	Induction/dose stabilization with Suboxone tablets (Cohort 4 only) for 7 days and titrated up to 12 mg	RBP-6000 Single dose Cohort 1: 50 (N=12) Cohort 2 100 (N=12) Cohort 3: 200 (N=12)	4 weeks (1 SC injection)	Opioid dependent (DSM-IV-TR) Treatment-seeking	Single center
MW: 13-0006	NCT02559973	SUBOXONE SL film Induction/dose stabilisation phase: 7-8 days, titrated up to 12 mg	RBP-6000 Single dose 300 PLGH A, low MW (N=16) PLGH B, high MW (N=15) PLGH C, intermediate MW (N=16)	4 weeks (1 SC injection)	Opioid dependent (DSM-IV-TR) Treatment-seeking	Single center
FTIH 10-0011	NCT02765867	None	RBP-6000 Single dose 20 (N=12)	4 weeks (1 SC injection)	Opioid dependent (DSM-IV-TR) Methadone Treatment-seeking	Single center

Source: Reviewer and Applicant’s Clinical overview (Table 1)

5.2. Review Strategy

For the efficacy evaluation, data from the Phase 3, double-blind, placebo-controlled, safety and efficacy study (13-0001) were examined. The Ph3DB study (13-001) study was intended to compare the efficacy of two dosing regimens of RBP-6000 300/300 mg (6 doses of 300 mg) and RBP-6000 300/100 mg (initial two doses of 300 mg followed by 4 doses of 100 mg) with that of placebo (matched volume ATRIGEL). Analyses of these data were performed by the primary Statistics Reviewer, Dr. Feng Li, who reproduced the Applicant's analyses to ensure that they were replicable and conducted additional analyses deemed important for efficacy ascertainment and for better understanding of the clinical relevance of the findings.

Additionally, the CSS Clinical reviewer Dr. Alan Trachtenberg, MD, MPH and Division of Biometrics VII statistical reviewer Dr. Wei Liu reviewed the opioid blockade study (13-0002) to assess whether the study supports efficacy.

For the safety evaluation, major safety results were from the Phase 3, double-blind, safety and efficacy trial (13-0001) and Phase 3, open-label, long-term safety study (13-0003). These two Phase 3 studies were evaluated individually and pooled for safety analysis. Additionally, safety data from the clinical pharmacology studies (2 Phase 2 MAD studies and 3 Phase 1 SD studies) were used to supplement and complement safety data.

A joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting was held on October 31, 2017 to discuss aspects of the Sublocade (RBP-6000) NDA submission pertaining to the efficacy findings, safety findings, and the proposed REMS recommendations.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Phase 3, double-blind, placebo-controlled, efficacy and safety trial (13-0001)

6.1.1. Study Design

Overview and Objective

The pivotal safety and efficacy study (13-0001) was designed to compare the effects of RBP-6000 with placebo. Two dosing regimens of RBP-6000 300/300 mg (6 doses of 300 mg) and RBP-6000 300/100 mg (two initial dose of 300 mg followed by four doses of 100 mg) were tested in the pivotal study. The study population was treatment-seeking patients with moderate-to-severe opioid use disorder as defined by DSM 5 diagnosis. After screening, eligible subjects entered a 2 week, open-label, run-in period. They were induced with Suboxone SL film

for 3 days, followed by an 11 day dose-adjustment period based on withdrawal symptoms to achieve a dosage range from 8 to 24 mg/day. Subjects who met randomization criteria were randomized into four groups to receive RBP-6000 (two dosing regimens) or placebo (two volume-matched doses) treatment for 24 weeks under double-blind conditions. The primary efficacy endpoint was the cumulative distribution function of the percentage weeks without illicit opioid use⁸ measured by weekly UDS (Urine Drug Screen) negative for opioids and self-reports negative for illicit opioid from Week 5 through 24. The key secondary endpoint was the proportion of subjects achieving treatment success (responder), which was defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 5 and Week 24.

Trial Design

The design and analysis of the pivotal clinical trial was discussed and agreed upon prior to conduct.

After 2 weeks open-label induction and dose- stabilization with Suboxone film, subjects who met randomization criteria that included no significant opioid craving (≤ 20 mm on an Opioid Craving VAS) or opioid withdrawal (a score of ≤ 12 on the COWS) after at least 7 days of SUBOXONE sublingual film treatment could then be randomized to study treatment.

Subjects who met the randomization criteria were randomized to treatment groups in a 4:4:1:1 ratio to 1 of 4 treatment regimens as follows (Figure 1):

- Regimen #1: RBP-6000 300 mg SC every 28 days (± 2) × 6 doses + IDC
- Regimen #2: RBP-6000 300 mg SC every 28 days (± 2) × 2 doses + IDC followed by RBP-6000 100 mg SC every 28 days (± 2) × 4 doses + IDC
- Placebo Regimen #1: Volume-matched to Regimen #1 + IDC
- Placebo Regimen #2: Volume-matched to Regimen #2 + IDC

Table 1 displays the composition of RBP 6000 300 mg and 100 mg and Table 8 displays the composition of RBP-6000 placebo 300 mg and 100 mg

Table 8: Composition of RBP-6000 placebo (100 mg and 300 mg)

Component	% Weight/Weight	100 mg Placebo	300 mg Placebo
Buprenorphine	0	0	0
50:50 Poly(DL-lactide-co-glycolide)	(b) (4)		
N-methyl-2-pyrrolidone	(b) (4)		
Total Formulation Delivered (mg)	(b) (4)		
Approximate Volume Delivered (mL)	-	0.5	1.5

⁸ Referred to in the protocol as “weeks of abstinence”

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

Source: RB-US-13-0001 CSR Table 3

A 24 week double-blind treatment period was chosen according to the Agency's recommendations. The Agency recommended 24 week treatment periods for the pivotal safety and efficacy trials supporting the approval of Probuphine and Vivitrol for the treatment of opioid dependence as well.

The initial 4 weeks of the double-blind treatment period were considered a "grace period" because patients may not respond immediately. Data on drug use from this period of time was not considered in the efficacy analysis. This is consistent with the Agency's previous recommendations for the pivotal clinical trials for Probuphine and Vivitrol.

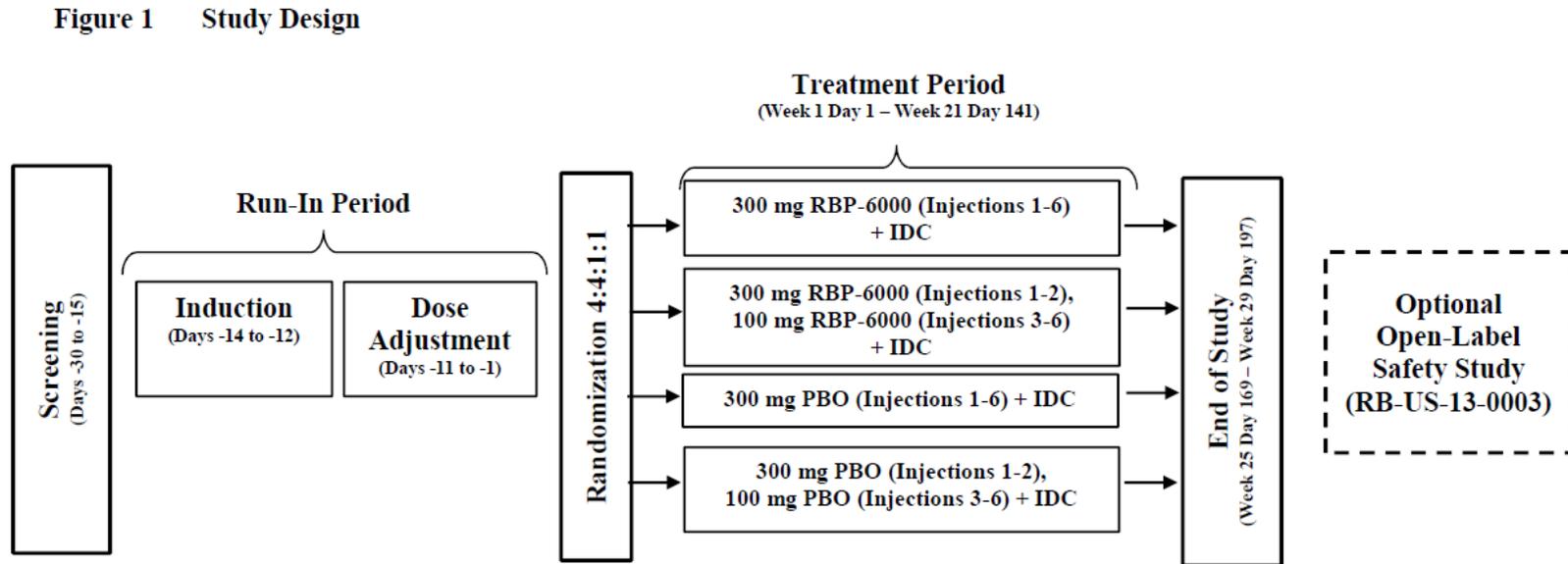
During the 24-week double-blind treatment period, subjects also received individual drug counseling (IDC), consisting of weekly manual-guided individual behavioral therapy as described in the study reference manual. This is consistent with the labeling of approved transmucosal buprenorphine products for the treatment of opioid use disorder to be used as part of a complete treatment plan to include counselling and psychosocial support.

Following randomization, subjects were to return to the clinic weekly for UDS, TLFB interviews, COWS, SOWS, Opioid Craving VAS and safety assessments. At injection visits, assessments using the CGI-I and CGI-S scales were performed. Health economics and outcomes research assessments were also conducted periodically. An additional blinded UDS could have been performed if abuse was suspected during the double-blind phase. Per the protocol, prior to the injection, an in-office benzodiazepine urine test could be performed if the investigator suspected possible benzodiazepine use. If the test was positive, the investigator was to contact the medical monitor or the sponsor to discuss whether or not to administer study treatment.

Upon the completion of the study, subjects could choose to participate the Phase 3 open-label, long-term, safety study (13-0003).

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Figure 3: Pivotal safety and efficacy study (13-0001) scheme



IDC=individual drug counselling

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

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

Study populations

A total of 504 subjects with moderate to severe opioid use disorder as defined by DSM-5 diagnosis, age 18-65, males and females were randomized in the study. Subjects selection criteria are listed below:

Inclusion criteria:

- Subject currently met DSM-5 criteria for moderate or severe opioid use disorder or by medical history, subject had met DSM-5 criteria for moderate or severe opioid use disorder for the 3 months immediately prior to signing the ICF
- Subject was seeking MAT for opioid use disorder.
- Body mass index (BMI) of ≥ 18.0 to ≤ 35.0 kg/m².
- Females: Women of childbearing potential (defined as all women who were not surgically sterile or postmenopausal for at least 1 year prior to informed consent) were required to have a negative pregnancy test prior to enrollment, and agreed to use a medically-acceptable means of contraception⁹ from screening through at least 6 months after the last dose of study treatment.
- Males: Male subjects with female partners of childbearing potential agreed to use medically-acceptable contraception after signing the ICF through at least 6 months after the last dose of study treatment. Male subjects also agreed not to donate sperm during the study and for 6 months after receiving the last dose of study treatment.
- Subject agreed not to take any buprenorphine products other than those administered during the current study throughout participation in the study

Exclusion Criteria

- Subject had a current diagnosis, other than opioid use disorder, requiring chronic opioid

• ⁹ The following methods of contraception were considered to be medically acceptable: established use of oral, injected or implanted hormonal contraception; placement of an intrauterine device or intrauterine system; use of a double-barrier method of contraception (condom or occlusive cap with use of a spermicide) or male sterilization.

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

treatment

- Subject had a current substance use disorder, as defined by DSM-5 criteria, with regard to any substances other than opioids, cocaine, cannabis, tobacco or alcohol.
- Subject had a positive UDS result at screening for cocaine or cannabis AND met DSM-5 criteria for either moderate or severe cocaine or cannabis use disorder, respectively.
- Subject met DSM-5 criteria for moderate or severe alcohol use disorder.
- Subject received MAT for opioid use disorder (e.g., methadone, buprenorphine) in the 90 days prior to providing written informed consent.
- Subject's treatment for opioid use disorder was required by court order
- Subject's current incarceration or pending incarceration/legal action that could have prohibited participation or compliance in the study
- Subject was a pregnant or lactating female.
- Subject required current use of prescription or over-the-counter (OTC) medications that were clinically relevant cytochrome P450 3A4 or cytochrome P450 2C8 inducers or inhibitors (e.g., rifampicin, azole antifungals [e.g., ketoconazole], macrolide antibiotics [e.g., erythromycin]) with the exception of marijuana.
- Subject had history of suicidal ideation within 30 days prior to providing written informed consent as evidenced by answering "yes" to questions 4 or 5 on the suicidal ideation portion of the eC-SSRS completed at the screening visit or history of a suicide attempt (per the eC-SSRS) in the 6 months prior to informed consent.
- Subject had current or history (within the 6 months prior to providing written informed consent) of chest pain or palpitation with either exertion or drug use, peripheral or generalized edema, clinically significant cardiovascular disease, including myocardial infarction, heart failure, uncontrolled hypertension, clinically significant orthostatic hypotension, endocarditis or myocarditis
- Subject had clinically significant abnormal systolic blood pressure (BP) or diastolic BP, in the opinion of the investigator
- Subject had uncontrolled medical or psychiatric illness that, in the opinion of the investigator or sponsor, may have placed the subject at risk or interfered with outcome measures or a subject's ability to participate in the study.

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

- Subject had clinically significant abnormality (e.g., severe respiratory insufficiency) in past medical history or at the screening physical examination that, in the opinion of the investigator or sponsor, may have placed the subject at risk or interfere with treatment outcomes.
- Subject had history or presence of allergic or adverse response (including rash or anaphylaxis) to buprenorphine, naloxone or the ATRIGEL Delivery System.
- Subject had participated in any other clinical trial within 30 days prior to informed consent
- Subject had total bilirubin $\geq 1.5 \times$ upper limit of normal (ULN), alanine aminotransferase (ALT) $\geq 3 \times$ ULN, aspartate aminotransferase (AST) $\geq 3 \times$ ULN, serum creatinine $> 2 \times$ ULN, international normalized ratio $> 1.5 \times$ ULN, lipase $> 3 \times$ ULN, amylase $> 3 \times$ ULN or any abnormal pancreatic enzyme value above ULN that was associated with a clinically significant, active pancreatic disorder
- Subject had congenital long QT syndrome, history of prolonged QT in the 3 months prior to screening or a corrected QT interval (Fridericia's corrected [for heart rate], QTcF) > 450 msec (male) or > 470 msec (female) or history of risk factors for Torsades de Pointes
- Subject had clinically significant anemia or low hemoglobin (levels < 9 g/dL) at screening or donation of > 250 mL of blood or plasma within the 30 days prior to providing written informed consent
- Subject had diagnosis of acquired immunodeficiency syndrome
- Subject had previously received RBP-6000
- Subject was affiliated with, or a family member of, site staff directly involved in the study.
- Subject was unable, in the opinion of the investigator or the medically responsible physician, to comply fully with the study requirements
- Subject had use of (within the past 30 days prior to providing written informed consent) or positive UDS result at screening for barbiturates, benzodiazepines, methadone or buprenorphine. If, after discussion with the subject, the investigator had reason to believe that a positive UDS for buprenorphine may have been due to a false-positive test result, a 1-time retest was allowed. This retest must have been performed within 48 hours of receipt of the initial buprenorphine UDS test result

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

Schedules of events

Table 7, Table 8 and Table 9 were adapted from CSR (13-0001) and contain the schedules of events for screening and SUBOXONE film induction, RBP-6000 Injection Visits 1 through 3, and RBP-6000 Injection Visits 4 through 6 through follow-up, respectively.

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

Table 9: Schedule of Events: Screening and SUBOXONE Sublingual Film Induction

Appears this way on original

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

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

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

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

Appears this way on original

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

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

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

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

6. Only for female subjects who were of childbearing potential (not postmenopausal or surgically sterile for at least 1 year).
7. Assessments should have been performed prior to each SUBOXONE sublingual film dosing and at approximately the same time each day (\pm 2 hours).
8. Included a review of previous (within 30 days prior to screening) and ongoing medications.
9. A PK sample was to be taken as soon as possible after any SAE was reported. If possible, an additional sample should have been collected when the SAE had resolved.
10. This visit became Day -1 if the following criteria were met:
 - no allergic reaction to SUBOXONE sublingual film
 - daily dose of SUBOXONE sublingual film between 8 mg/2 mg to 24 mg/6 mg (inclusive) buprenorphine/naloxone
 - a COWS score of \leq 12
 - an Opioid Craving VAS score of \leq 20 mmIf Day -1 criteria were met, the subject was scheduled the following day (Injection Visit #1/Day 1) to receive the first injection of study treatment after randomisation criteria were met.
11. If Day -1 criteria were not met after 14 days of SUBOXONE sublingual film treatment and a subject still had significant withdrawal signs/symptoms and opioid cravings (COWS score $>$ 12 and Opioid Craving VAS $>$ 20 mm), they were not eligible to continue in the study. They were provided with information on the options for opioid use disorder treatment.
12. Blood sampling for PK assessments started on Day -1 in subjects who met Day -1 criteria. See PK table (see [Appendix 4](#) of the protocol in Appendix 16.1.1) for exact time points. A resting 12-lead ECG was taken \leq 60 minutes prior to the first PK sample collected on Day -1.
13. SUBOXONE sublingual film dosing should have taken place at the same time of day (\pm 2 hours).
14. Subjects should have been in opioid withdrawal (COWS score $>$ 12) prior to receiving the first dose of SUBOXONE sublingual film on Day -14.
15. Subjects should **not** have taken their dose of SUBOXONE sublingual film until after it had been determined if they had met Day -1 criteria (see footnote #10 for specific criteria).
16. Performed only on Day -1.

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

Table 10: Schedule of Events: RBP-6000 Injection Visits 1–3

Appears this way on original

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

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

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

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

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

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

Evaluation	Inj 1	Postinjection 1 Assessments							Inj 2	Postinjection 2 Assessments				Inj 3	Postinjection 3 Assessments			
	Wk1 D 1	Wk1 D 2	Wk1 D 3*	Wk1 D 4*	Wk1 D 5*	Wk2 D 8	Wk3 D 15	Wk4 D 22	Wk5 D 29	Wk5 D 30	Wk6 D 36	Wk7 D 43	Wk8 D 50	Wk9 D 57	Wk9 D 58	Wk10 D 64	Wk11 D 71	Wk12 D 78
Window		+1	NA	NA	NA	±1	±1	±1	±2	+1	±1	±1	±1	±2	+1	±1	±1	±1
Employment Status and Health Insurance	X ¹⁷								X ¹⁷					X ¹⁷				
HCRU	X ¹⁷								X ¹⁷					X ¹⁷				

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

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

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

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

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

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

Table 11: Schedule of Events: RBP-6000 Injection Visits 4–6, End of Study/Early Termination Visit and Follow-up

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

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

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

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Evaluation	Inj 4	Postinjection 4 Assessments				Inj 5	Postinjection 5 Assessments				Inj 6	Postinjection 6 Assessments				EOS/ET/ Safety Follow-up	
	Wk13 D 85	Wk13 D 86	Wk14 D 92	Wk15 D 99	Wk16 D 106	Wk17 D 113	Wk17 D 114	Wk18 D 120	Wk19 D 127	Wk20 D 134	Wk21 D 141	Wk21 D 142	Wk22 D 148	Wk23 D 155	Wk24 D 162	Wk25 D 169 ¹⁷	Wk29 D 197 ¹⁸
Window	± 2	+ 1	± 1	± 1	± 1	± 2	+ 1	± 1	± 1	± 1	± 2	+ 1	± 1	± 1	± 1	± 2	± 2
AE Assessment ¹⁰	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
eC-SSRS (Since last-visit-version) ¹¹	X		X	X	X	X		X	X	X	X		X	X	X	X	
TLFB Interview ¹¹	X		X	X	X	X		X	X	X	X		X	X	X	X	X
Opioid Craving VAS ¹¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
COWS ¹¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SOWS ¹¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CGI-S ¹¹	X					X					X					X	
CGI-I ¹¹	X					X					X					X	
BDI-II ¹¹	X					X					X					X	
BPI ¹¹	X					X					X					X	
Study Treatment Injection	X					X					X						
Injection Site Grading Scale ¹²	X	X				X	X				X	X					
Injection Site Pain VAS ¹³	X					X					X						
Injection Site Evaluation ¹⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Behavioural Therapy ¹⁵	X		X	X	X	X		X	X	X	X		X	X	X	X	
EQ-5D-5L											X ¹⁶					X	
SF-36v2											X ¹⁶					X	
MSQ											X ¹⁶					X	
Employment Status and Health Insurance	X ¹⁶					X ¹⁶					X ¹⁶					X	
HCRU	X ¹⁶					X ¹⁶					X ¹⁶					X	

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

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

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

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

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

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

Study Endpoints

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Primary efficacy endpoint: the cumulative distribution function of the percentage of weekly UDS negative for opioids and self-reports negative for illicit opioid use¹⁰ from week 5 through 24. The primary efficacy endpoint is a clinically relevant surrogate endpoint used previously by the division as a basis for approval of Vivitrol .

Major efficacy outcome measurements included weekly UDS and TLFB. Self-reports of illicit opioid use were obtained from Timeline Follow Back (TLFB) interviews. UDS tests were performed by (b) (4) using EMIT II Plus assays (Siemens Healthcare Diagnostics), DRI Oxycodone Assay (Thermo Fisher Scientific) and CEDIA Buprenorphine Assay (Thermo Fisher Scientific) (Table 12). GC/MS (Gas chromatography/mass spectrometry) were used for the confirmatory tests if UDS tested positive for opioids. As shown in the Table 13, opioids detected in the UDS confirmatory test included methadone, codeine, morphine, hydrocodone, oxycodone, hydromorphone and oxymorphone. Fentanyl, if present, would not be detected.

Table 12: Urine Drug Screen immunoassays (Applicant’s table)

Table 7 Urine Drug Screen Immunoassays

Drug/Drug Class	Cut-off (ng/mL)	Calibrator
Amphetamine	1000	d-Methamphetamine
Barbiturates	300	Secobarbital
Benzodiazepines	300	Lorazepam
Buprenorphine	5	Buprenorphine
Cannabinoids	50	11-nor-delta9-THC-9-COOH
Cocaine Metabolite	300	Benzoylcegonine
Methadone	300	Methadone
Opiates	300	Morphine
Oxycodone	300	Oxycodone
Phencyclidine	25	Phencyclidine
Source:	(b) (4)	

¹⁰ Referred to in the protocol as “abstinence”

Table 13: Urine Drug screen confirmatory testing information (Applicant’s table)

Table 8 Urine Drug Screen Confirmatory Testing Information

Methodology	Confirmation Component	Cut-off (ng/mL)	Calibrator (ng/mL)	Hydrolysis (Yes or No)	Limit of Detection (ng/mL)	Limit of Quantitation (ng/mL)	Limit of Linearity (ng/mL)
GC/MS	Methadone	300	300	No	100	100	3000
GC/MS	Codeine	50	300	Yes	50	100	4000
	Morphine	50	300	Yes	50	100	2000
	Hydrocodone	50	300	Yes	50	100	3000
	Hydromorphone	50	300	Yes	50	100	2000
	Oxycodone	50	300	Yes	50	100	3000
	Oxymorphone	50	300	Yes	50	100	2000

Abbreviation: GC/MS=Gas chromatography/mass spectrometry

Key secondary efficacy endpoint: responder rate or treatment success rate. Responder or treatment success was defined as any subject with $\geq 80\%$ of urine samples negative for opioids combined with self-reports negative for illicit opioid use (from the TLFB interview) between Week 5 and Week 24

Additional secondary efficacy endpoints

- The CDF of the percentage of urine samples negative for opioids from Week 5 through Week 24
- The CDF of the percentage of self-reports negative for illicit opioid use from Week 5 through Week 24
- Change from baseline in the opioid craving score using the Opioid Craving VAS from Week 5 through Week 24
- Percentage of completers (a completer was defined as a subject who completed the Week 24 visit, either the UDS or TLFB assessment);
- Percentage of subjects abstinent (i.e., having urine samples negative for opioids as well as self-reports negative for illicit opioid use by TLFB interview) at Week 24 and in the following week intervals: Weeks 5-8, 9-12, 13-16, 17-20 and 21-24;
- score on the CGI-I scale from Week 5 through Week 24;
- score on the CGI-S scale from Week 5 through Week 24;

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

- total score on the COWS from Week 5 through Week 24;
- total score on the SOWS from Week 5 through Week 24;
- total number of weeks of abstinence as assessed from urine samples negative for opioids combined with self reports

In addition to efficacy endpoints, the study also evaluated PK of RBP-6000 (100 mg and 300 mg SC injections), effects of RBP-6000 on PD outcomes, pharmacogenomics (PGx) of RBP-6000-treated-subjects, and effects of RBP-6000 on health economic and outcomes research endpoints.

Statistical Analysis Plan

The Applicant defined analysis populations or sets used for data analyses as the following:

“Full Analysis Set: The Full Analysis Set (FAS) was comprised of all randomized subjects. This population was used for all efficacy analyses. For these analyses, subjects were analyzed as randomized and not according to treatment actually received

Per Protocol Set: The Per Protocol Set (PPS) was used for supportive efficacy analyses and was comprised of all randomized subjects who received at least 1 dose of study treatment and did not have any important protocol deviations during the study.

Run-in Safety Set: The Run-in Safety Set (RSS) was comprised of all enrolled subjects who received at least 1 dose of SUBOXONE sublingual film during the run-in phase.

Safety Analysis Set: The Safety Analysis Set (SS) was comprised of all enrolled subjects who received at least 1 dose of randomized study treatment. This population was used for all safety analyses. In the safety analyses, subjects were analyzed according to treatment actually received.”

Site 20 was excluded from primary and key secondary efficacy analyses due to compliance issues, but was included in all safety analyses

Table 14 Analysis Populations/Sets

Analysis Set	Total	RBP-6000		Placebo+IDC
		300mg/100mg+IDC	300mg/300mg+IDC	
Full Analysis Set ¹	504	203	201	100
Excluding Site 20	489	194	196	99
Per Protocol Analysis Set ¹	457	185	183	89
Run-In Safety Set ²	665			
Safety Analysis Set ^{1,3}	504	203	201	100

IDC = individual drug counselling

¹ Full analysis set and per protocol analysis set were analysed as randomised. Safety analysis set was analysed as treated.

² Includes subjects who received at least 1 dose of SUBOXONE sublingual film during the run-in phase.

³ Includes subjects who received at least 1 dose of randomised study treatment in the double-blind phase.

Source: Table 14.1.1.4

Primary efficacy analysis strategy per protocol

The primary null (H_0) and research hypotheses (H_a) for primary efficacy endpoint were as follows:

- H_0 : Neither of the 2 dose regimens of RBP-6000 (dose Regimen #1: 6 × 300 mg or dose Regimen #2: 2 × 300 mg + 4 × 100 mg) is superior to placebo at Week 24 with respect to the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use collected from Week 5 through Week 24, examined as a CDF
- H_a : At least 1 of the 2 dose regimens of RBP-6000 (dose Regimen #1: 6 × 300 mg + or dose Regimen #2: 2 × 300 mg + 4 × 100 mg) is superior to placebo at Week 24 with respect to the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use collected from Week 5 through Week 24, examined as a CDF

The primary efficacy analysis was performed in the FAS using the 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. The Wilcoxon rank-sum test was used to compare the treatment groups. To test the two primary hypotheses, a truncated Hochberg procedure was used with a truncation parameter of 0, which reduces to Bonferroni. Therefore, the 2 primary hypotheses were tested at $\alpha = 0.025$ level.

Table 14: Derivation of the composite primary efficacy endpoints

Urine Drug Screen Result ¹	Self-Report of Illicit Opioid Use Result ^{1,2}	Primary Efficacy Endpoint
Non-negative	Non-negative	Non-negative
Non-negative	Negative	Non-negative
Negative	Non-negative	Non-negative
Negative	Negative	Negative

¹Missing urine drug screen samples and/or self-reports were counted as non-negative.

²The self-reports of illicit opioid use were obtained from Timeline Followback (TLFB) interviews.

Key secondary efficacy analysis strategy per protocol

The null (H_{10}) and research hypotheses (H_{1a}) for the key secondary efficacy endpoint of treatment success were:

H_{10} : Neither of the 2 dose regimens of RBP-6000 is superior to placebo with respect to treatment success.

H_{1a} : At least 1 of the 2 dose regimens of RBP-6000 is superior to placebo with respect to treatment success.

The Cochran-Mantel-Haenszel (CMH) test was used to test the difference in treatment success rates.

Missing data imputation strategy

Missing UDS samples and/or self-reports (including missing assessments from prematurely discontinued subjects) were imputed as non-negative.

The Agency agreed on the proposed analysis strategy and the missing data imputation strategy for the primary efficacy endpoint and key secondary efficacy endpoint. Please refer to the statistical review by Dr. Feng Li for details.

Protocol Amendments

The original protocol was submitted on 10/21/2014. Two protocol amendments were submitted on 6/16/2015 and 8/21/2015 respectively.

In Protocol amendment 1, submitted on 6/16/2015, changes to the protocol included: summary of study results of opioid blockade study, rationale for dose selection, study population selection and administrative changes. Study population selection criteria was revised responding to Agency's recommendations. The revised study selection criteria in response to Agency's

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

feedback included: Exclusion Criterion #5 was revised to exclude subjects who have received medication-assisted treatment for opioid use disorder within 90 days (instead of 30 days) prior to providing written informed consent. Exclusion Criterion #17 was revised to ensure exclusion of subjects with coagulopathy or significant pancreatic abnormalities.

In the Protocol amendment 2 submitted on 8/21/2015, the protocol was revised in response to Agency's feedback. In the revised protocol, all randomized subjects who receive an injection of RBP-6000 or placebo will begin a 5-day SUBOXONE sublingual film taper on Day 1. This taper is intended to preserve the blind of the study and to mitigate potential withdrawal signs and symptoms in placebo-treated subjects. Approximately 1/3 of patients received Suboxone tapering after the protocol amendments.

6.1.2. Study Results

Compliance with Good Clinical Practices

According to the Applicant, RB-US-13-0001, the main trial supporting this application, was conducted in accordance with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) guidelines and all applicable regulations, including, where applicable, the Declaration of Helsinki. The Applicant also documented that the trial was conducted in keeping with applicable national and local laws and regulations. This appears to be consistent with the OSI inspection reports.

Financial Disclosure

The Applicant's submission included the completed "Certification: Financial Interests and Arrangements of Clinical Investigators" form (Form FDA 3455). The Applicant indicated that the investigators at each site are certified as having no Financial Arrangement as defined in 21 CFR 54.2.

Patient Disposition

A total of 504 subjects were randomized into the study. A total of 201 subjects were randomized to the RBP-6000 300 mg/300 mg group and 203 subjects were randomized to the RBP-6000 300 mg/100 mg group and 100 subjects were randomized to the placebo groups as shown in Table 15. More than 60 % of subjects in RBP-6000 treatment group completed the study and only 34% of subjects in placebo group completed the study. The most common reasons for early discontinuation in the RBP-6000 treatment group included lost to follow up (~12%), subject withdrew consent (~10%) and other reasons (more than 3%). The most common reasons for discontinuation in the placebo group included lack of efficacy (18%),

subject withdrawal of consent (12%) and lost to follow up (12%). The percentage of subjects who dropped out due to “lack of efficacy” and “subjects withdrew consent” was higher in the placebo group than RBP-6000 treatment group. The percentage of loss to follow up was similar between the RBP-6000 treatment group and placebo group. Discontinuation due to “other” includes site closed by the Applicant (n=9), incarceration (n=7), relocation (n=4), noncompliance with study visits/lost to follow-up type reasons.

Table 15 Subject Disposition All Screened Subjects (Study 13-0001)

Category	Total	RBP-6000 300mg/100mg+IDC (N=203) n (%)	RBP-6000 300mg/300mg+IDC (N=201) n (%)	Placebo+IDC (N=100) n (%)
Randomized	504	203 (100.0)	201 (100.0)	100 (100.0)
Randomized and treated	504	203 (100.0)	201 (100.0)	100 (100.0)
Completed	288	125 (61.6)	129 (64.2)	34 (34.0)
Discontinued	216	78 (38.4)	72 (35.8)	66 (66.0)
Reasons for discontinuation				
Lost to follow-up	61	26 (12.8)	23 (11.4)	12 (12.0)
Subject withdrew consent to participate	59	20 (9.9)	21 (10.4)	18 (18.0)
Other ^a	30	17 (8.4)	6 (3.0)	7 (7.0)
Lack of efficacy	26	3 (1.5)	5 (2.5)	18 (18.0)
Adverse event	18	6 (3.0)	10 (5.0)	2 (2.0)
Protocol deviation	7	2 (1.0)	5 (2.5)	0 (0.0)
Withdrawal symptoms	5	1 (0.5)	1 (0.5)	3 (3.0)
Noncompliance with study drug	4	2 (1.0)	0 (0.0)	2 (2.0)
Subject was withdrawn by the investigator	4	1 (0.5)	0 (0.0)	3 (3.0)
Physician decision	2	0 (0.0)	1 (0.5)	1 (1.0)
Death ^p	0	0 (0.0)	0 (0.0)	0 (0.0)

IDC = individual drug counselling, N = total number of subjects exposed; n = number of subjects in a subset in a

Source: Applicant’s summary of clinical efficacy Table 8

Protocol Violations/Deviations

Per the Applicant’s subject disposition table, a total of 7 subjects dropped out early due to protocol deviations with 2 subjects from RBP-6000 300/100 mg group and 5 subjects from RBP-6000 300/300 mg group. The Applicant provided the protocol deviations datasets for the pivotal study. Recorded protocol violations were categorized into 13 categories including: inclusion criteria, exclusion criteria, study drug Suboxone, study drug RBP-6000, assessment safety lab/EKG, assessment efficacy, visit window, assessment timing, informed consent, prohibited concomitant medications, PK assessment and SAE reporting. Table 7 summarizes the distribution of protocol violations. The most frequently recorded protocol violations included assessment timing, visit window, PK assessment, which are not likely to influence conclusions about efficacy. The percentage of subjects with protocol deviations related to the efficacy

assessments was evenly distributed across RBP-6000 treatment groups and placebo group. Protocol deviations related to the efficacy assessments included missed urine samples or UDS tests, missed behavior therapy, missed COWS, pain, VAS assessments etc. Missed urine sample or UDS tests are considered important for the primary efficacy endpoints analysis. A total of 43 missed 48 UDS tests during treatment period week 1 and week 24 were recorded and summarized in **Table 18**. The reasons for the missing samples were inspected and classified as being due to site or medical staff errors, and not necessarily informative, or being due to the subject's behavior (e.g, refused, left early, unable to void), and therefore, given the typical course of OUD treatment, very possibly indicative of illicit drug use. For the purposes of this analysis, samples missing due to staff/site errors could be considered missing data at random (MAR), and those due to subject behavior could be considered missing data not at random (MNAR). A total of 17 subjects had UDS tests that could be classified as MAR, while 26 subjects had UDS tests that were classified as MNAR. Because the protocol-specified analyses treated all missing samples as positive, an imbalance in the number of samples that were missing truly at random could influence the interpretation of the data. The statistician reviewer Dr. Feng Li conducted a sensitivity analysis which determined that the impact of these protocol deviations was minor.

Table 16: Distribution of protocol violation

DVDECOD	Phase 3 DB (13-0001)					
	PBO		RBP300/100 mg		RBP 300/300 mg	
	N=100		N=203		N=201	
	N	%	N	%	N	%
Assessment Timing	84	84%	184	91%	183	91%
Assessment Safety Lab/ECG	63	63%	147	72%	148	74%
Visit Window	60	60%	143	70%	151	75%
PK Assessment	47	47%	146	72%	119	59%
Study Drug - Suboxone	41	41%	93	46%	70	35%
Assessment Efficacy	24	24%	52	26%	42	21%
Inclusion Criteria	10	10%	12	6%	15	7%
Prohibited Con Med	7	7%	13	6%	15	7%
Informed Consent	6	6%	15	7%	10	5%
Study Drug - RBP 6000	5	5%	7	3%	10	5%
Exclusion Criteria	0	0%	7	3%	3	1%
SAE Reporting	1	1%	0	0%	0	0%

Source: Reviewer generated from dataset ADPD

Table 17: Protocol violation due to UDS missing

	Phase 3 DB (13-0001)					
	PBO		RBP300/100 mg		RBP 300/300	
	N=100		N=203		N=201	
UDS missing data category	N	%	N	%	N	%
MAR	3	3%	7	3%	7	3%
NMAR	3	3%	10	5%	13	6%

Table of Demographic Characteristics

As shown in Table 19, the baseline characteristics (Age, Sex and Race) of the populations were evenly distributed across the RBP-6000 treatment arms (RBP-6000 300/100 mg and RBP-6000 300/300 mg) and placebo arms in the Phase 3 double blind controlled study (13-0001). Most subjects in the study were white males with an average age of approximately 40 years old. More than 40 % of subjects reported injection drug use in the past. More than 50% of subjects reported a history of polysubstance abuse. These demographic and baseline characteristics are very typical for the treatment population with OUD.

Table 18: Demographic characteristics of the study population (13-0001)

	RBP-6000 100 mg (N=203)	RBP-6000 300 mg (N=201)	Placebo (N=100)
Age (days)			
Mean (SD)	40 (11)	39 (11)	39 (11)
Median	38	38	38
Min, Max	19, 64	19, 64	20, 63
Sex, n (%)			
Male	136 (67%)	135 (67%)	65 (65%)
Female	67 (33%)	66 (33%)	35 (35%)
Race, n (%)			
White	140 (69%)	144 (72%)	78 (78%)
Black or African American	57 (28%)	55 (27%)	20 (20%)
American Indian or Alaska Native	4 (2%)	1 (0%)	1 (1%)
Asian	0	0	0
Multiple	2 (1%)	1 (0%)	1 (1%)
Weight at screening (kg)			
Mean (SD)	77 (16)	80 (17)	76 (16)
Median	75	78	73
Min, Max	46, 123	45, 128	48, 132
Baseline BMI (kg/m ²)			
Mean (SD)	25 (4)	26 (4)	25 (4)

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Median	25	26	25
Min, Max	18, 35	18, 35	18, 35

Substance use at screening			
Opioid use –injectable route	90 (44%)	84 (42%)	50 (50%)
Tobacco	187 (92%)	186 (93%)	93 (93%)
Alcohol	160 (79%)	160 (80%)	81 (81%)
Drug use history			
Cannabinoids	113 (56%)	95 (47%)	53 (53%)
Cocaine	94 (46%)	80 (40%)	42 (42%)
Amphetamine/Methamphetamine	53 (26%)	29 (14%)	19 (19%)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline characteristics of drug use history seem congruent with the target U.S. population for marketing. **Table 20** displays baseline drug use history distribution in Phase 3 DB study (13-001). Approximately 50% subjects reported history of cannabinoid use, 40% subjects reported a history of cocaine use and 15% subjects reported a history of Amphetamine/Methamphetamine use.

Table 19: Baseline drug use history distribution (13-0001)

	PBO		RBP-100		RBP-300	
	N=100		N=203		N=201	
Drug use history	N	%	N	%	N	%
Any Drug Use History	100	100%	203	100%	201	100%
Opioids	100	100%	203	100%	201	100%
Cannabinoids	53	53%	113	56%	95	47%
Cocaine	42	42%	94	46%	80	40%
Amphetamines/Methamphetamine	19	19%	53	26%	29	14%
Methadone	5	5%	25	12%	14	7%
Benzodiazepines	13	13%	25	12%	20	10%
Buprenorphine	6	6%	20	10%	16	8%
Barbiturates	0	0%	3	1%	1	0%
Other Substance	1	1%	2	1%	6	3%
Phencyclidine	1	1%	0	0%	2	1%

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

CDER Clinical Review Template
 Version date: September 6, 2017 for all NDAs and BLAs

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

Treatment compliance was considered to be adequate as active drugs or placebos were administered by health care providers in clinical settings at monthly visits (28 days \pm 2 days) during the clinical development program. There were subjects who received monthly injections one week earlier or later than the scheduled visits. However, the PK data appears not to be impacted. During the actual treatment period, no rescue buprenorphine was allowed.

Permitted concomitant medications per protocol:

After the randomizations, Ibuprofen, acetaminophen, methocarbamol, hydroxyzine and loperamide were permitted to be administered to subjects to help alleviate signs and symptoms of opioid withdrawal as deemed necessary by the investigator or medically qualified sub-investigator.

Prohibited concomitant medications per protocol:

- Transmucosal buprenorphine (during the treatment period after the randomization)
- P450 3A4 inducers or inhibitors, such as azole antifungals (e.g., ketoconazole) or macrolide antibiotics (e.g., erythromycin)
- Herbal supplements that had the potential to cause prolongation of the QTc interval or other possible toxic /undesirable effects
- Any OTC medications with the potential to cause prolongation of the QTc interval
- ANY medications may have been expected to significantly interfere with the metabolism or excretion of buprenorphine that may have been associated with a significant drug interaction with buprenorphine, or may have posed a significant risk to subjects' participation in the study.

Efficacy Results – Primary Endpoint

Primary efficacy endpoint analysis was performed by the statistical reviewer Dr. Feng Li. The primary efficacy endpoint was analyzed using the Wilcoxon rank-sum test. Efficacy analyses were conducted for the full analysis population (FAS), excluding subjects from site 20 due to compliance issues. The two randomized placebo groups were combined and analyzed as one placebo group. Missing UDS samples and self-reports were imputed as positive in the primary analysis. The two RBP-6000 dose regimens were each tested against placebo at the 0.025 level. As shown in Table 21 and Figure 4, the difference between the two dosing regimens and placebo in the distribution function was statistically significant with p -value <0.0001 for each dose of the active treatment based on the Wilcoxon rank-sum test. About 12-13% of patients in each active treatment group had no positive or missing samples or self-report of illicit use over the 20-week efficacy ascertainment period.

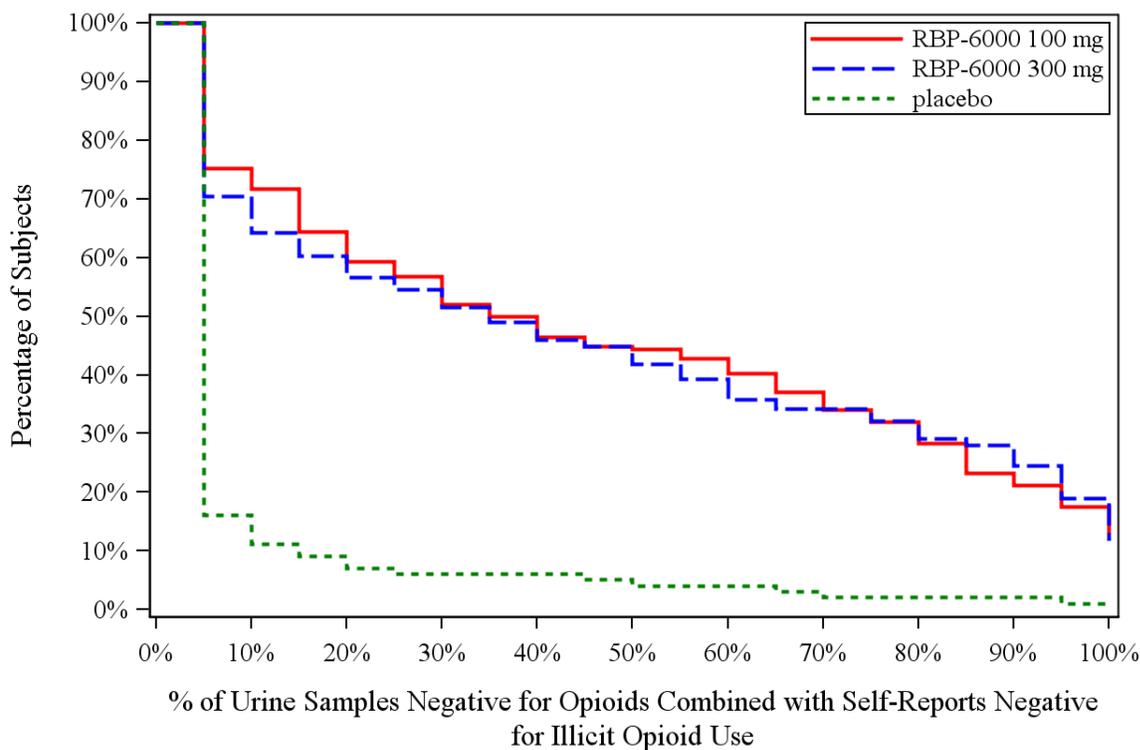
CDER Clinical Review Template
Version date: September 6, 2017 for all NDAs and BLAs

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 20: Cumulative percentage of negative opioid use from week 5-24

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

Figure 4: Cumulative distribution function of percentage negative use



The limitation of Figure 4 is that the overall percent of negative tests does not differentiate between, for example, a patient who is abstinent for half the study and then relapses to daily illicit drug use, a patient who continues to use illicit drugs daily for half the study and then stops completely, and a patient who uses intermittently, half the days throughout the study. All of these patients might have 50% of their tests negative. To allow an appreciation of the temporal sequence of patients' test results, the graphic depictions at subject levels (Figure 5) show the results of each urine test for each patient. They also distinguish between tests that were imputed as positive in the analyses because they were intermittent missing, or because a patient self-reported drug use, and actual positive tests.

As shown in Figure 5, each individual subject is represented along the y-axis. On the x-axis are the time points during which urine samples were collected. (In this study, urine samples were collected weekly). Blue circular dots are used to represent submission of opioid- negative urine samples at any time point, while red triangular dots are used to represent opioid-positive urine submissions. Ideally, a patient achieving treatment success would have many more blue data points than red data points, particularly along the right-hand side of the x-axis which represents

longer periods of time on treatment. The data points that appear black in these presentations are '+' symbols and denote intermittent missing urine data. The red "x" dots indicate where urine samples were negative or missing but subjects self-reported opioids use.

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

Figure 5: Urine Opioid screen results for individual subjects

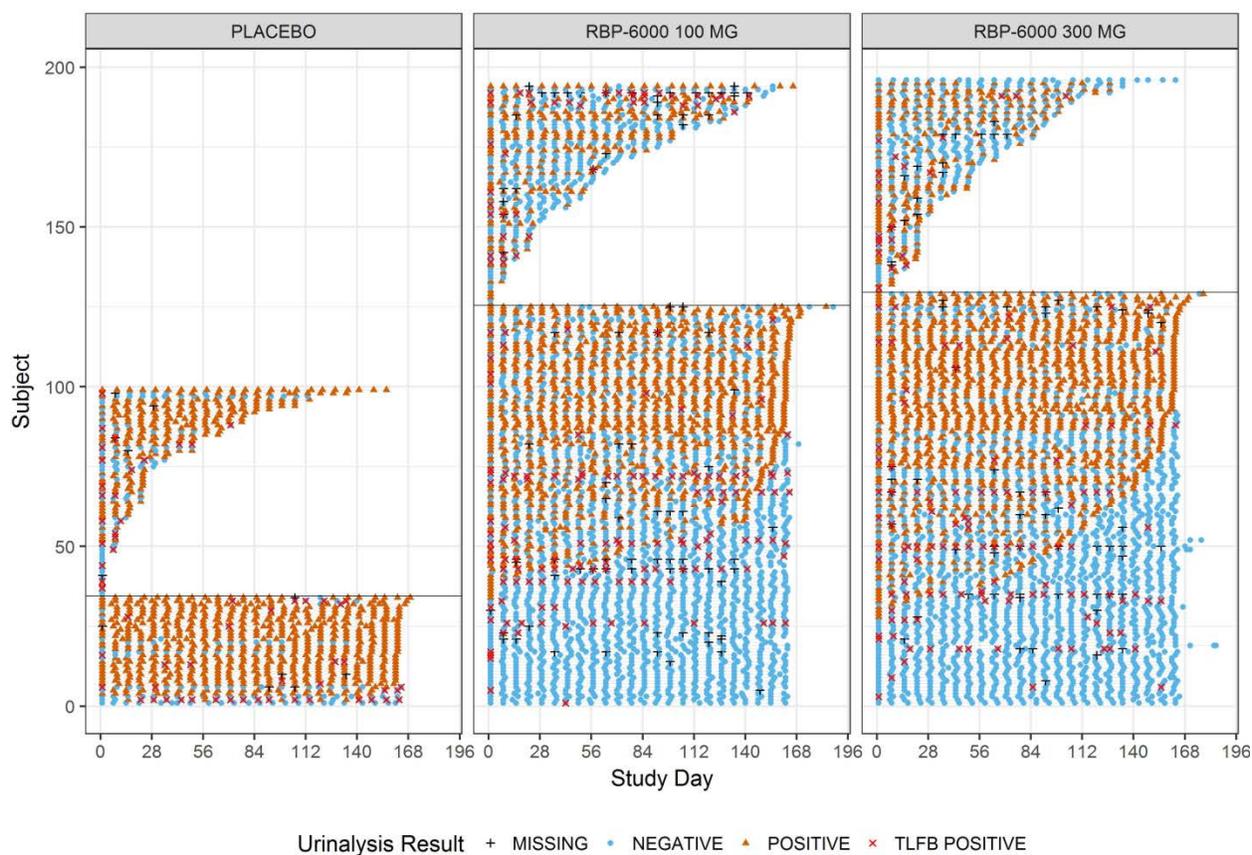


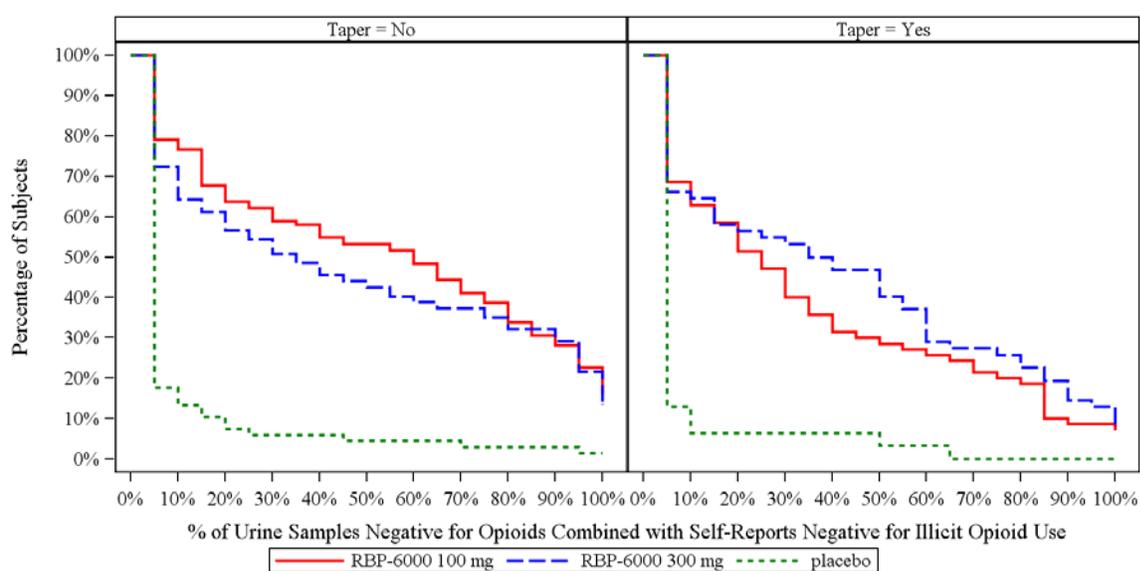
Table 22 illustrates the degree of concordance between urine test findings and self-report. This tabulation shows that the self-report of drug use was negative on over half the occasions on which the patient submitted a sample which was positive. Self-report contributed to detecting drug use in the presence of a negative urine sample in only about 5% of occasions. Notably, only 35% of positive UDS results were accompanied by a self-report of use, suggesting that UDS is an important aspect of collection of data on drug use.

Table 21: UDS results vs TLFB week 5 to week 24 (Excluding site 20)

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

After the study was initiated, the protocol was amended to incorporate a taper at the end of the sublingual film run-in to mitigate the potential effects of abrupt discontinuation on patients blindly switched to placebo injections, which could increase the rate of discontinuations in the placebo arm and lead to a spurious conclusion about efficacy in that arm. A total of 163 (32%) subjects received a 5-day SUBOXONE sublingual film taper following the first injection of study treatment. The cumulative distribution functions of percentage abstinence are depicted by tapering status in Figure 12. The figures illustrate that there was no obvious difference in retention in the placebo group based on presence or absence of tapering.

Figure 6: CDF of the percentage abstinence for subjects by tapering status



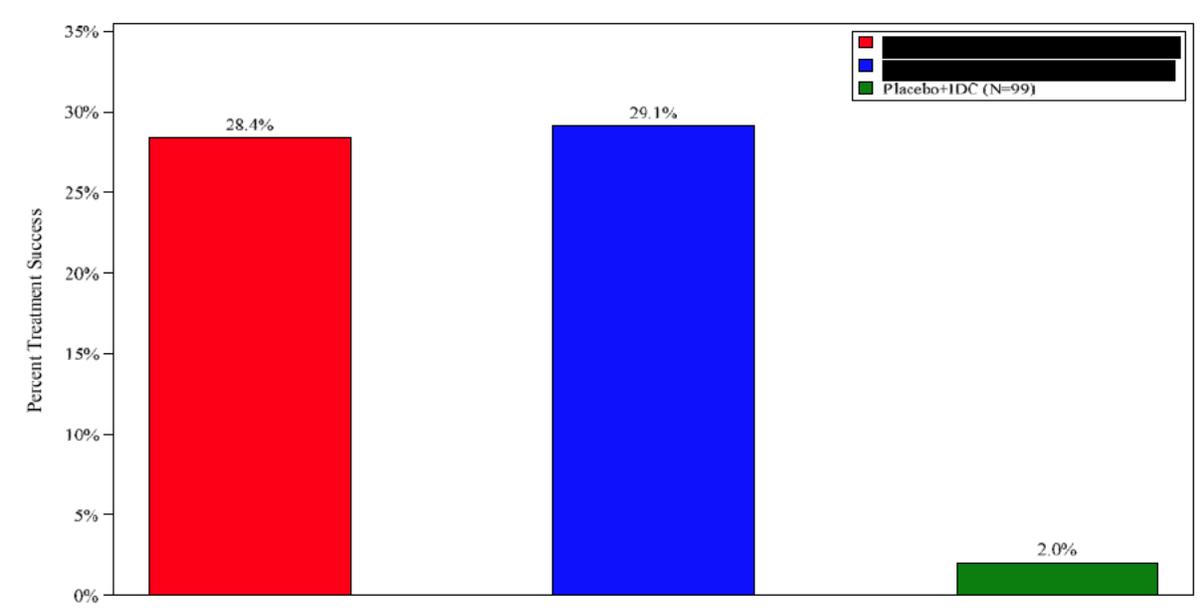
Data Quality and Integrity

The submission was adequately organized and did not present barriers to review.

Efficacy Results – Secondary and other relevant endpoints

Key secondary endpoint analysis was performed in the full analysis sets excluding subjects from site 20. The pre-specified responder definition allowed four missing or positive samples out of the 20 collected. The proportion of patients meeting that criterion as well as the proportion who had no indicators of illicit use were both higher in each of the active treatment groups than the placebo group with nominal statistical significance based on Fisher's Exact test. Responder rate or treatment success rate was statistically significantly higher in both the 300 mg/100 mg and 300 mg/300 mg groups compared with the placebo group; 28.4% and 29.1% compared to 2.0%, respectively ($P < 0.0001$ for each of the 2 active treatment groups compared with placebo).

Figure 7: Key secondary efficacy endpoints: percentage of subjects meeting criteria for responder or treatment success

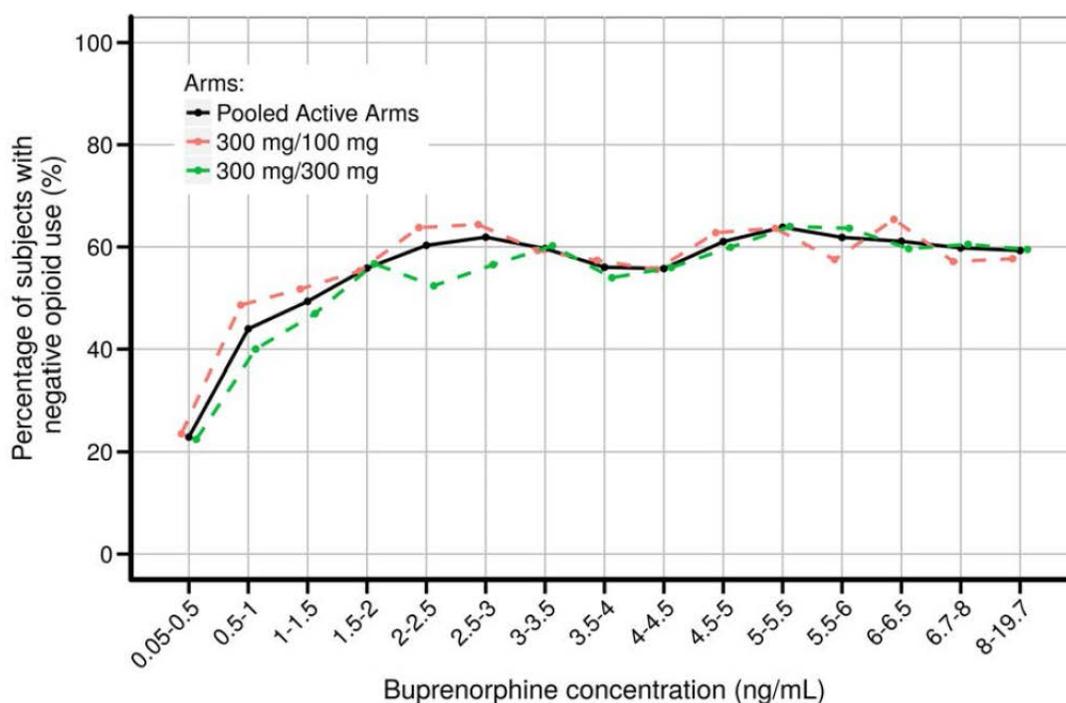


Subjects received RBP-6000 containing 300 mg buprenorphine for the first 2 injections, 4 injections of RBP-6000 containing 100 mg buprenorphine.

Dose/Dose Response

The efficacy has been demonstrated in both primary efficacy endpoint and key secondary endpoint for both dosing regimens of RBP-6000 300/300 mg and RBP-6000 300/100 mg. Both dosing regimens were equally effective. The Applicant assembled plots to display the relationship between negative opioid use and buprenorphine plasma concentration in Study 13-0001. The observed data regarding negative opioid use and buprenorphine plasma exposure indicate a plateau of maximal response at approximately 2 ng/ml (Figure 8). There is an apparent “plateau” of where these responses are at their maximum at a range above 2-3 ng/ml.

Figure 8: Relationship Between the Proportion of Subjects with Negative Opioid Use and Buprenorphine Plasma Concentration (Study 13-0001)



Curves=percentage of subjects with negative opioid use in the 300 mg/100 mg arm (red curve), 300 mg/300 mg arm (green curve) and for the 2 arms pooled (black curve)

Source: [INDV-6000-M04 Figure 9](#)

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

The statistical reviewer Dr. Feng Li performed a subgroup analysis by injection drug use status, incorporating the UDS results. It appears that injection drug users numerically responded to

the high dose regimen RBP-6000 300/300 mg better than RBP-6000 300/100 mg based on the CDF curve plot below (Figure 9 and Figure 10). However, the difference was not statistically significant.

Figure 9: CDF of percentage abstinence for injection drug users

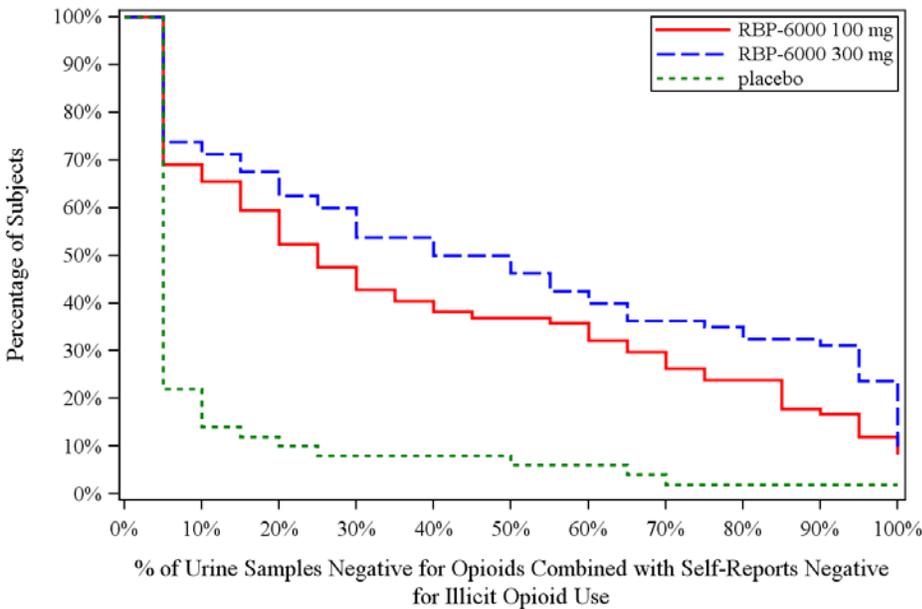
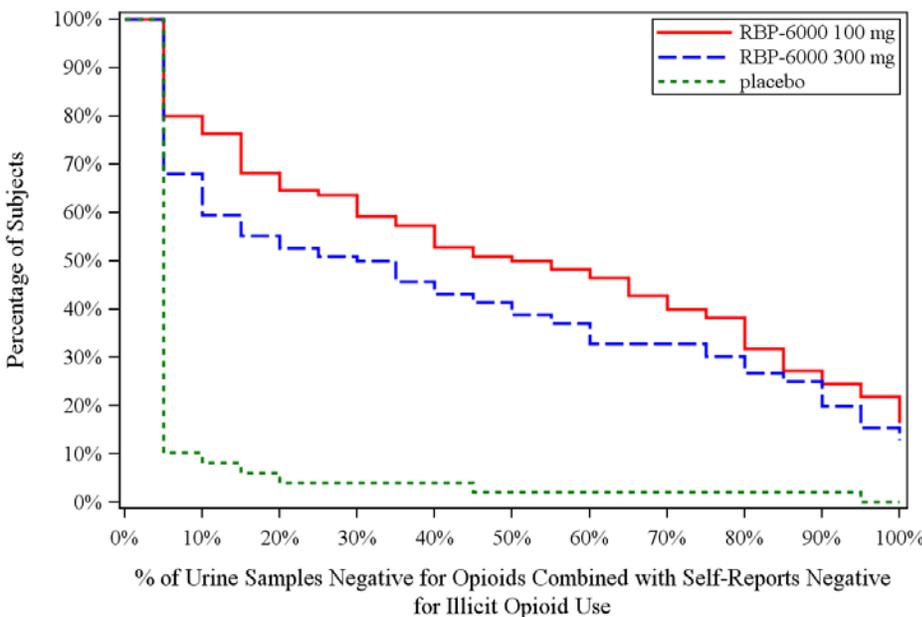


Figure 10: CDF of percentage abstinence for non-injection drug users



Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

Durability of Response

The pivotal efficacy study is a 24-week treatment clinical trial. Efficacy of RBP-6000 beyond 24 weeks has not been studied.

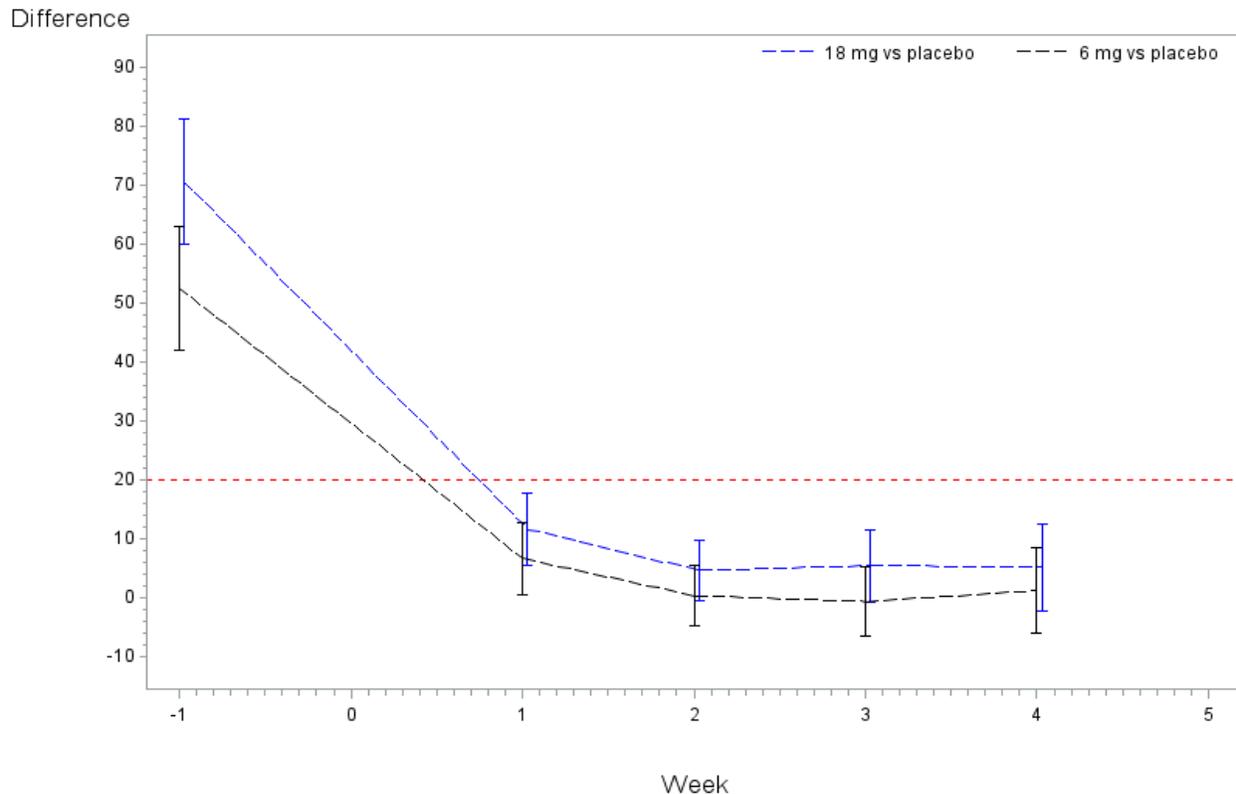
Efficacy Summary

The efficacy has been demonstrated in both primary efficacy endpoint and key secondary endpoint for both dosing regimens RBP-6000 300/300 mg and RBP-6000 300/100 mg. Both dosing regimens were equally effective. Treatment differences between the 300/300-mg or 300/100-mg group and the placebo group were similar among most of the clinical subgroups of interest (age, sex, race, and BMI) as summarized in the Applicant's table and Dr. Feng Li's statistics review. The efficacy results are further supported by PK and PD population modeling results as both of the proposed dosing regimens (300 mg / 100 mg) and (300 mg / 300 mg) appear to be able to, on average, achieve exposures throughout the dosing interval that achieve the maximum effect on self-reported drug use and block or substantially attenuate the subjective responses to opioids. Exposure-response analyses for negative opioid use indicate that subjects who used illicit opioids via the injectable route had a 3.6 times greater EC₅₀ (4.3 ng/mL) than the EC₅₀ for subjects who used illicit opioids via other routes (1.2 ng/mL). Subgroup analysis indicated that subjects with A history of injection drug use responded numerically better to the high dose regimen RBP -6000 300/300 mg than low dose regimen RBP-6000 300/100 mg, but the difference was not statistically significant.

6.2. Opioid blockade study (RB-US-13-0002)

Study title: 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 was reviewed by CSS reviewer Dr. Alan Trachtenberg, MD, MPH. Please refer to his review for the study design, study conduct and study results. They concluded that: "The test product (RBP-6000) at 300 mg after the first injection showed blockade effect for hydromorphone (6 mg and 18 mg) using E-max model (Unipolar scale) (Figure 11).

Figure 11: Mean Difference of Emax (in Unipolar Scales) between Hydromorphone and Placebo over Weeks (Non-inferiority margin I=20) (Generated by CSS statistic reviewer)



The pharmacometric reviewer Dr. Bewernitz performed PK/ PD analysis of the data from the opioid blockade study. He concluded that PK/PD data analysis results provides supportive evidence of opioid blockade trend of drug-liking reduction with increasing buprenorphine exposure. There was a trend of drug-liking reduction with increasing buprenorphine exposure (Figure 13). Higher buprenorphine concentrations were required to reduce drug-liking after 18 mg than for 6 mg hydromorphone challenge (Figure 12 and Figure 13).

Figure 12: Placebo-Corrected Drug-Liking By Time and Hydromorphone Dose Level

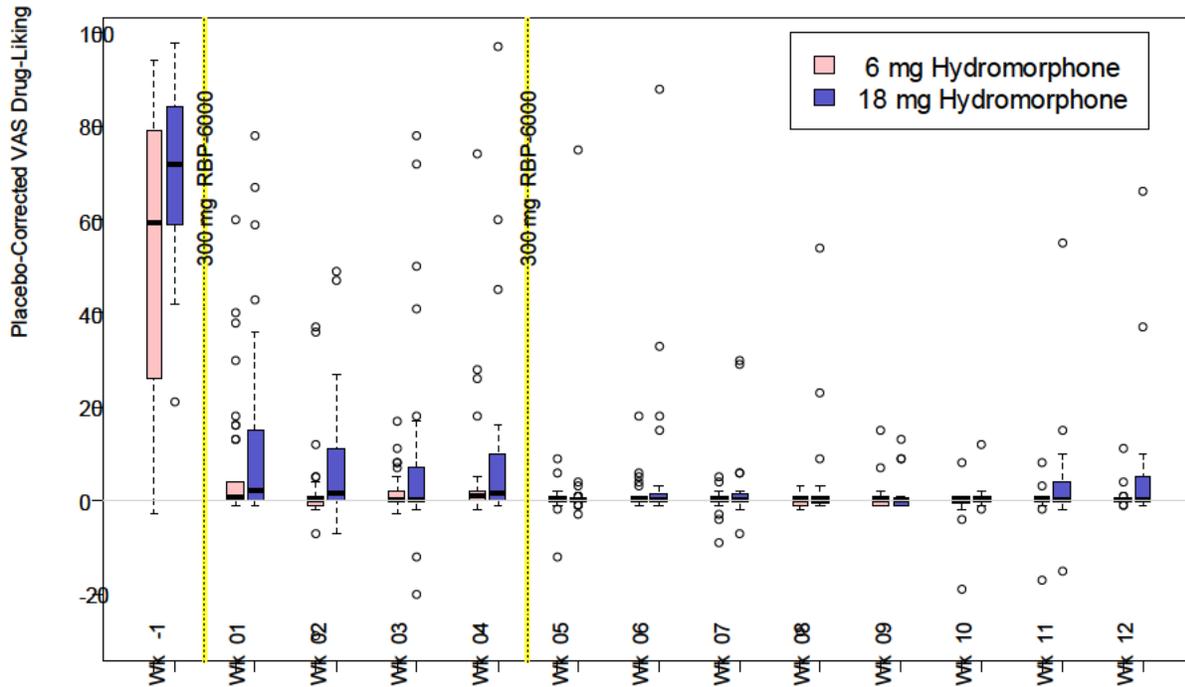
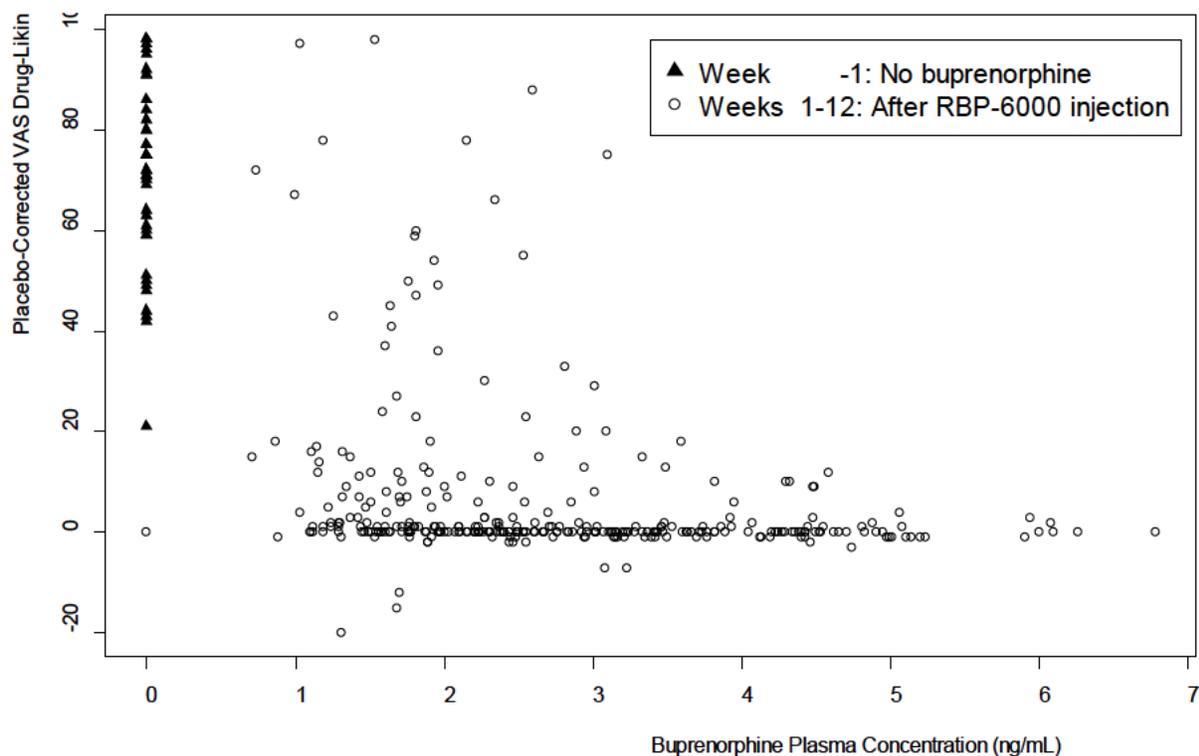


Figure 13: Placebo-Corrected Drug-Liking vs. Associated Buprenorphine Concentration (Response to 18 mg Hydromorphone Challenge)



7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Efficacy data from opioid blockade study (13-002) and Phase 3 pivotal, double-blind, placebo-controlled study (13-0001) provide evidence that both dosing regimens of RBP-6000 are effective in treating patients with opioid use disorder. The opioid blockade study (13-0002) determined that the 300 mg dose of RBP-6000 was able to block the drug liking response to exogenous opioids using hydromorphone challenge tests and the 300 mg dose of RBP-6000 was subsequently used for the pivotal efficacy study (13-0001). There is only one pivotal efficacy study (13-0001) relevant to this treatment paradigm, so no integrated review of effectiveness was performed.

Efficacy Discussion

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

This program was undertaken with advice from the Division. Indivior was advised to target a plasma buprenorphine level that completely blocked the effects of exogenous opioids at clinically-relevant doses. A study showing this effect, taken together with compelling results from a single outpatient controlled clinical trial showing the efficacy of the product in treating patients with opioid dependence could potentially be considered, taken together, as substantial evidence of efficacy.

Indivior performed initial studies of receptor occupancy to determine the doses to evaluate in the blockade study. Having demonstrated the blockade effect of the 300 mg dose, Indivior then undertook a clinical study comparing six monthly doses of 300 mg vs two monthly doses of 300 mg with subsequent reduction to 100 mg, vs placebo in patients initially titrated to a stable dose with sublingual buprenorphine. This initial stabilization on daily-dosed medication prior to depot treatment is a customary approach to use of depot medications in other therapeutic areas.

The design and analysis of the blockade study were agreed to with the Division and the Controlled Substances Staff prior to the study. This is a somewhat novel study but employs customary approaches used in evaluations of human abuse liability.

The design and analysis of the outpatient clinical trial was also discussed and agreed upon prior to conduct. There is currently no standard approach to clinical trials in this therapeutic area. Previously approved products were supported by a variety of studies with treatment as long as 40 weeks, and various analytic approaches were applied in evaluating the results.

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

Several other features were incorporated into this program to address the difficulties of retaining patients in treatment and to address the concern that patients may be clinically successful despite occasional lapses in abstinence. These include the following:

- Less frequent urine testing

Historically, studies of opioid dependence treatment have incorporated thrice-weekly urine sampling. This frequency was identified as providing the best balance between detecting all

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

use and avoiding false-positive tests due to “carry-over” positives, based on the time window of detection for heroin, which was the most commonly-used opioid in populations being studied when this approach was established. Additionally, this approach was not considered unduly burdensome because the treatments being evaluated were agonists that were administered in-clinic on a daily basis.

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

Indivior’s clinical studies employed weekly urine testing. This infrequent sampling inherently allows patients who are not fully abstinent to be adjudicated as successful, even if the definition of response is 100% negative samples, because some use will not be detected. We accept this for reasons of feasibility.

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

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

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

One compromise approach that the Division has proposed is to perform an analysis that considers the full range of responder definitions, from complete abstinence to no abstinence, but to emphasize the effect of the drug on promoting abstinence or near-abstinence. This approach, the continuous responder curve, or the cumulative distribution function (CDF) of drug use assessments, was employed in this program. The continuous responder curve gives an overall picture of the drug’s effect on drug use behavior. Augmenting this analysis with a responder rate comparison ensures that the effect is of a magnitude that has clinical meaningfulness.

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

In Indivior’s study, there were weekly, scheduled, samples collected over 24 weeks. However, the first month is considered a “grace period” because patients may not respond immediately. A CDF of patient responses was the primary endpoint, and the secondary endpoint was a responder analysis. The responder definition agreed to was 80% negative. Therefore, a responder is defined as a patient who provides self-report and laboratory evidence of absence of illicit opioid use on 16 of 20 scheduled weekly visits. Such patients may have a number of undetected occasions drug use; however the ability to attend study visits and provide negative urine samples over a 24-week period is nevertheless an indicator of some degree of clinical stability.

Notably, even using a responder definition of 100% of urine samples and self-reports present and negative, both regimens of RBP-6000 were shown to be superior to placebo. Contrary to many assumptions, the retention rate in the placebo group, while low, was not zero. Over one-third of the placebo-treated subjects completed the full 24 weeks of the study. However, the response rate even in completers was very low.

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

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

8. Review of Safety

8.1. Safety Review Approach

The Applicant's submission included safety data from two Phase 3 studies, two Phase 2 multiple dose studies and three Phase 1 single dose studies. Table 23 displays the planned dose level and population size for each study. Safety data from the Phase 3 double-blind, placebo controlled, 24 -weeks efficacy and safety study (13-0001) and the Phase 3 open -label, long- term safety and tolerability study (13-0003) were primarily used to support the NDA approval. Safety data from the Phase 1 and 2 studies were used as supplement and complement the safety data from the key studies.

Table 22: Safety database for RBP-6000

Safety database for RBP-6000						
	Study ID	Study design	RBP-6000 Dose (mg)	Injections (Planned)	Sample size	Conduction time
Phase 1	RB-US-10-0011	FIH	20	SD	12	11/30/2010-05/31/2011
	RB-US-10-0020	SAD	50	SD	12	07/10/2012-02/16/2013
			100	SD	27	
			200	SD	12	
RB-US-13-0060	MW	300	SD	16	09/22/2015-02/10/2016	
		300(Low MW)	SD	16		
		300 (high MW)	SD	16		
Phase 2	RB-US-12-0005	MAD	50	4 injections	15	10/5/2012-05/04/2014
			100	4 injections	30	
			200	4 injections	30	
			300	4 injecttions	14	
	RB-US-13-0002	OB, MD	300	2 injections	39	11/19/2013-07/29/2014
Phase 3	RB-US -13-0001	MD, DB,PC	300/300	6 injections	201	01/28/2015-04/29/2016
			300/100	6 injections	203	
			PBO	6 injections	100	
	RB-US-13-0003	OL, long term (Ongoing)	De novo	12 injections	412	7/27/2015-08/12/2016
			300/flex			
			Roll over	6 injections	257	
			300/flex			

The safety evaluation of RBP-6000 centered on an assessment of the systemic effects of the active ingredient, buprenorphine, in this sustained release formulation. The other principal focus was on the local injection tolerability of RBP-6000 as it relates to injection site reactions. The safety profile of the drug substance, buprenorphine, has been fairly well-characterized. Given that RBP-6000 provides higher levels of exposure to buprenorphine than the approved transmucosal formulations, on which the safety profile is based, an adequate safety database was needed to characterize effects of higher doses of RBP-6000 when it is indicated for chronic treatment of opioid use disorder. The Applicant was advised to provide a safety database meeting the recommendation of the International Conference on Harmonization (ICH) for the CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

size of safety data base to characterize the safety profiles for new drugs, and the extent of exposure in submitted safety data does meet those recommendations. Review of the RBP-6000 safety data did not identify major systemic safety concerns beyond those consistent with the established safety profile of buprenorphine. As such, a primary focus of this discussion will be on the formulation-specific safety findings and the local injection toxicity unique to this novel buprenorphine delivery system. The difference of the safety profiles between high dose regimen RBP-6000 300/300 mg and low dose regimen RBP-6000 300/100 mg will be discussed. Safety topic of special interest included injection site reactions, hepatic effects, CNS depression, respiratory depression, cardiac conduction effects, and orthostatic hypotension. Acute pancreatitis was included as a topic of special interest due to a nonclinical safety finding of pancreatic acinar cell apoptosis.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 1083 subjects, ages 18-65 years, with opioid use disorder or opioid dependence received at least 1 SC injection of RBP-6000 across 7 studies over the clinical development program (Table 23). A total of 235 subjects in Phase 1 and 2 studies received RBP-6000 single dose or multiple doses ranging from 20 to 300 mg with 196 subjects at the 100 mg, 200 mg or 300 mg dose.

A total of 848 subjects received at least one dose of RBP-6000 300 mg in pooled Phase 3 studies (13-0001 and 13-0003). In the Phase 3 double blind, placebo controlled study (13-0001), a total of 504 treatment-seeking patients with moderate-to-severe opioid use disorder (OUD) as defined by DSM-5 diagnosis were randomized to receive either RBP-6000 or placebo SC injection for 24 weeks under double blind conditions after a 2 weeks open-label induction and dose adjustment phase with Suboxone film. A total of 201 subjects were randomized into the RBP-6000 300/300 group to receive 6 planned doses of RBP-6000 300 mg and 203 subjects in the RBP-6000 300/100 group to receive 2 doses of 300 mg initially and 4 doses of 100 mg subsequently. The study design of the Phase 3 open-label, long-term safety study (13-0003) was similar to the Phase 3 double-blind study (13-0001). A total of 669 subjects with OUD participated in the actual treatment period after a 2-week run in period with Suboxone film in the Phase 3 open-label, long term safety study (13-0003) and they were planned to receive an initial dose of 300 mg and subsequent doses could be 300 mg or 100 mg monthly, based on clinician judgment. A total of 257 subjects were Roll-over subjects from the Phase 3 DB study (13-0001) and were planned to receive an initial dose of 300 mg and followed by up to 5 additional injections for a total of 6 injections. Additionally, 412 subjects were de novo subjects and were planned to receive an initial dose of 300 mg and followed by up to 11 additional injections for a total of 12 injections.

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

The NDA Data cutoff date was Aug 12, 2016 and the Phase 3 open label, long-term safety study (13-0003) was still ongoing. The Applicant provided a preliminary safety update regarding SAEs, TEAEs and TEAEs leading to drug discontinuation in the NDA submission. Upon Agency request, the Applicant provided an updated exposure summary by including safety data after the NDA data cutoff date. As summarized in the updated tables provided by the Applicant on Sep 20, 2017 (Table 24, Table 25, and Table 26), a total of 565 (66.6%) subjects received more than 6 injections at doses of 300 mg and 100 mg, and 395 (43.3 %) subjects received 12 injections at doses of 300 mg and 100 mg. Cumulatively, a total of 542 (63.9%) subjects were exposed to RBP-6000 at monthly doses of 300mg and 100 mg for more than 24 weeks and 320 (37.7%) subjects were exposed to RBP-6000 at monthly doses of 300 mg and 100 mg for more than 48 weeks. A total of 187 (22.1%) subjects cumulatively were exposed to RBP-6000 at monthly doses of 300mg for more than 48 weeks. The safety database for both dose regimens (RBP 6000 300/100 mg and 300/300 mg) met ICH criteria for the treatment of chronic disease.

Table 23: Injections received by treatment group in Phase 3 studies

Exposure	13-0001 (Phase 3 DB)			13-0003 (Phase 3 OL)			De novo	All Phase 3 (13-0001 & 13-0003)
	RBP-6000 300/100 (N=203)	RBP-6000 300/300 (N=201)	PBO (N=100)	Roll-over				
				RBP-6000 100- RBP-6000 300/Flex (N=112)	RBP-6000 300- RBP-6000 300/Flex (N=113)	PBO- RBP-6000 300/Flex (N=32)		
Number of Injections, n (%)								
1	27 (13.3)	26 (12.9)	40 (40.0)	1 (0.9)	5 (4.4)	2 (6.3)	46 (11.2)	101 (11.9)
2	15 (7.4)	15 (7.5)	10 (10.0)	4 (3.6)	7 (6.2)	2 (6.3)	24 (5.8)	56 (6.6)
3	11 (5.4)	12 (6.0)	7 (7.0)	6 (5.4)	7 (6.2)	2 (6.3)	27 (6.6)	52 (6.1)
4	9 (4.4)	14 (7.0)	4 (4.0)	5 (4.5)	6 (5.3)	0	20 (4.9)	43 (5.1)
5	13 (6.4)	5 (2.5)	4 (4.0)	1 (0.9)	6 (5.3)	0	15 (3.6)	31 (3.7)
6	128 (63.1)	129 (64.2)	35 (35.0)	95 (84.8)	82 (72.6)	26 (81.3)	15 (3.6)	75 (8.8)
7	0	0	0	0	0	0	13 (3.2)	20 (2.4)
8	0	0	0	0	0	0	10 (2.4)	20 (2.4)
9	0	0	0	0	0	0	9 (2.2)	22 (2.6)
10	0	0	0	0	0	0	5 (1.2)	16 (1.9)
11	0	0	0	0	0	0	9 (2.2)	17 (2.0)
12	0	0	0	0	0	0	219 (53.2)	395 (46.6)

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 24: Cumulative treatment exposure by weeks in Phase 3 studies

Exposure	13-0001 (Phase 3 DB)			13-0003 (Phase 3 OL)			De novo RBP-6000 300/Flex (N=412)	All Phase 3 (13-0001 & 13- 0003) Total* RBP-6000 (N=648)
	RBP-6000 300/100 (N=203)	RBP-6000 300/300 (N=201)	PBO (N=100)	Roll-over				
				RBP-6000 100- 300/Flex (N=112)	RBP-6000 300- 300/Flex (N=113)	PBO- RBP-6000 300/Flex (N=32)		
Duration of Exposure (Cumulative categories; Weeks), n (%)								
>= 4 Weeks	203 (100)	201 (100)	100 (100)	112 (100)	113 (100)	32 (100)	412 (100)	848 (100)
>= 8 Weeks	171 (84.2)	171 (85.1)	57 (57.0)	110 (98.2)	105 (92.9)	29 (90.6)	359 (87.1)	730 (86.1)
>=12 Weeks	157 (77.3)	157 (78.1)	50 (50.0)	105 (93.8)	100 (88.5)	28 (87.5)	338 (82.0)	680 (80.2)
>=16 Weeks	150 (73.9)	144 (71.6)	42 (42.0)	100 (89.3)	93 (82.3)	26 (81.3)	309 (75.0)	629 (74.2)
>=20 Weeks	137 (67.5)	132 (65.7)	39 (39.0)	96 (85.7)	86 (76.1)	26 (81.3)	293 (71.1)	588 (69.3)
>=24 Weeks	75 (36.9)	97 (48.3)	26 (26.0)	65 (58.0)	63 (55.8)	16 (50.0)	278 (67.5)	542 (63.9)
>=28 Weeks	1 (0.5)	0	0	0	1 (0.9)	0	260 (63.1)	485 (57.2)
>=32 Weeks	0	0	0	0	0	0	248 (60.2)	466 (55.0)
>=36 Weeks	0	0	0	0	0	0	243 (59.0)	450 (53.1)
>=40 Weeks	0	0	0	0	0	0	233 (56.6)	427 (50.4)
>=44 Weeks	0	0	0	0	0	0	228 (55.3)	412 (48.6)
>=48 Weeks	0	0	0	0	0	0	187 (45.4)	320 (37.7)

Table 25: Cumulative exposure by dose level in Phase 3 studies

Exposure	RBP-6000	
	100 mg (N=313) n (%)	300 mg (N=848) n (%)
Duration of Exposure (Cumulative categories; Weeks)		
>= 4 Weeks	313 (100)	848 (100)
>= 8 Weeks	276 (88.2)	735 (86.7)
>=12 Weeks	238 (76.0)	621 (73.2)
>=16 Weeks	203 (64.9)	555 (65.4)
>=20 Weeks	107 (34.2)	498 (58.7)
>=24 Weeks	80 (25.6)	460 (54.2)
>=28 Weeks	60 (19.2)	392 (46.2)
>=32 Weeks	46 (14.7)	349 (41.2)
>=36 Weeks	29 (9.3)	265 (31.3)
>=40 Weeks	11 (3.5)	242 (28.5)
>=44 Weeks	4 (1.3)	210 (24.8)
>=48 Weeks	0	187 (22.1)

8.2.2. Relevant characteristics of the safety population:

As shown in Table 27, the baseline characteristics (Age, Sex and Race) of the populations were evenly distributed across the RBP-6000 treatment arms (RBP-6000 300/100 mg and RBP-6000 300/300 mg) and placebo arms in the Phase 3 double-blind controlled study (13-0001). Most subjects in the study were white males with an average age of approximately 40 years old. In the Phase 3 open-label, long term safety study (Table 28), subjects in the Roll-over group were, on average, two years older than the average age.

Table 26: Baseline demographic for Phase 3 DB study (13-0001)

Demographic Parameters	RBP100 (N=203) n(%)	RBP300 (N=201) n(%)	PLB (N=100) n(%)	Total (N=504) n(%)
SEX				
Male	136 (67.0)	135 (67.2)	65 (65.0)	336 (66.7)
Female	67 (33.0)	66 (32.8)	35 (35.0)	168 (33.3)
AGE				
Mean years (SD)	39.9 (11.3)	39.2 (11.0)	39.1 (10.9)	39.5 (11.1)
Median (years)	38	38	38	38
Min, Max (years)	19, 64	19, 64	20, 63	19, 64
AGE GROUP				
< 30	44 (21.7)	45 (22.4)	23 (23.0)	112 (22.2)
>=30 < 45	88 (43.3)	95 (47.3)	45 (45.0)	228 (45.2)
>=45 < 60	64 (31.5)	53 (26.4)	30 (30.0)	147 (29.2)
>=60	7 (3.4)	8 (4.0)	2 (2.0)	17 (3.4)
RACE				
White	140 (69.0)	144 (71.6)	78 (78.0)	362 (71.8)
Black	57 (28.1)	55 (27.4)	20 (20.0)	132 (26.2)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian	4 (2.0)	1 (0.5)	1 (1.0)	6 (1.2)
Native Hawaiian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (1.0)	1 (0.5)	1 (1.0)	4 (0.8)
Missing Race	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ETHNICITY				
Hispanic	13 (6.4)	18 (9.0)	10 (10.0)	41 (8.1)
Non-Hispanic	190 (93.6)	183 (91.0)	90 (90.0)	463 (91.9)
Missing Ethnic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

Appears this way on original

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

Table 27: Baseline demographic for Phase 3 OL, long-term study (13-0003)

Appears this way on original

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 6.3 Baseline Demographics for Phase III open label, long term safety study (13-0003)

Demographic Parameters	RBP-6000 DE NOVO (N=412) n(%)	RBP-6000 ROLL-OVER (N=257) n(%)	Total (N=669) n(%)
SEX			
Male	263 (63.8)	169 (65.8)	432 (64.6)
Female	149 (36.2)	88 (34.2)	237 (35.4)
AGE			
Mean years (SD)	38.4 (12.1)	41.6 (11.1)	39.6 (11.8)
Median (years)	36	40	38
Min, Max (years)	19, 65	21, 64	19, 65
AGE GROUP			
< 30	122 (29.6)	40 (15.6)	162 (24.2)
>=30 < 45	157 (38.1)	114 (44.4)	271 (40.5)
>=45 < 60	107 (26.0)	89 (34.6)	196 (29.3)
>=60	26 (6.3)	14 (5.4)	40 (6.0)
RACE			
White	295 (71.6)	168 (65.4)	463 (69.2)
Black	107 (26.0)	85 (33.1)	192 (28.7)
Asian	2 (0.5)	0 (0.0)	2 (0.3)
American Indian	2 (0.5)	2 (0.8)	4 (0.6)
Native Hawaiian	0 (0.0)	1 (0.4)	1 (0.1)
Other	6 (1.5)	1 (0.4)	7 (1.0)
Missing Race	0 (0.0)	0 (0.0)	0 (0.0)
ETHNICITY			
Hispanic	43 (10.4)	16 (6.2)	59 (8.8)
Non-Hispanic	369 (89.6)	241 (93.8)	610 (91.2)
Missing Ethnic	0 (0.0)	0 (0.0)	0 (0.0)
REGION			
United States	412 (100.0)	257 (100.0)	669 (100.0)
Rest of the World	0 (0.0)	0 (0.0)	0 (0.0)
Canada	0 (0.0)	0 (0.0)	0 (0.0)
South America	0 (0.0)	0 (0.0)	0 (0.0)
Europe	0 (0.0)	0 (0.0)	0 (0.0)
Asia	0 (0.0)	0 (0.0)	0 (0.0)
Africa	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

Baseline Medical history in Phase 3 studies

Table 29 summarizes the top 10 reported medical histories in the study population at baseline. As summarized in **Table 29**, the most frequent reported baseline medical histories by preferred term in the study population included Drug abuse, Back pain, Hepatitis C, Hypertension, Depression, Drug dependence, Anxiety, Insomnia, Asthma and Seasonal allergy. More than 10% of subjects reported a history of hepatitis C at the baseline. These baseline characteristics are very typical for the treatment population with opioid use disorder.

Baseline BMI distribution in Phase 3 studies

Table 30 displays the BMI distribution at baseline in the Phase 3 studies. Approximately 50% of subjects had normal BMI (18.5-25), 30% of subjects were overweight (BMI:25-30) and 20 % of subjects were obese (BMI \geq 30) in Phase 3 studies. The RBP-6000 300/300 group had the highest percentage of obese subjects (28%) compared with other groups. Per the Applicant, the impact of BMI on drug absorption is minimal.

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 28: Baseline medical history distribution in Phase 3 studies

Preferred term	Phase 3 DB (13-0001)						Phase 3 Open-label (13-0003)							
	PBO		RBP300/100 mg		RBP 300/300		De novo 300/Flex		PBO Roll-over 300/Flex		RBP 100 Roll-over 300/Flex		RBP 300 Roll over 300/Flex	
	N=100		N=203		N=201		N=412		N=32		N=112		N=113	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Drug abuse	88	88%	169	83%	162	81%	363	88%	29	91%	90	80%	92	81%
Hypertension	12	12%	32	16%	31	15%	49	12%	8	25%	20	18%	17	15%
Hepatitis C	10	10%	32	16%	24	12%	60	15%	4	13%	20	18%	18	16%
Depression	14	14%	28	14%	23	11%	60	15%	7	22%	14	13%	12	11%
Drug dependence	11	11%	25	12%	31	15%	46	11%	3	9%	17	15%	16	14%
Back pain	13	13%	31	15%	32	16%	40	10%	5	16%	14	13%	13	12%
Anxiety	10	10%	23	11%	22	11%	44	11%	4	13%	7	6%	9	8%
Insomnia	6	6%	23	11%	27	13%	40	10%	2	6%	8	7%	11	10%
Asthma	6	6%	12	6%	16	8%	35	8%	1	3%	3	3%	10	9%
Seasonal allergy	10	10%	11	5%	17	8%	16	4%	3	9%	7	6%	10	9%

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 29: Baseline BMI group distribution in Phase 3 studies

BMI group	Phase 3 DB (13-0001)						Phase 3 Open-label (13-0003)							
	PBO		RBP300/100 mg		RBP 300/300		De novo 300/Flex		PBO Roll-over 300/Flex		RBP 100 Roll-over 300/Flex		RBP 300 Roll over 300/Flex	
	N=100		N=203		N=201		N=412		N=32		N=112		N=113	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
> 0 to < 18.5	3	3%	6	3%	2	1%	9	2%	0	0%	4	4%	4	4%
>= 18.5 to < 25	46	46%	99	49%	88	44%	206	50%	14	44%	50	45%	46	41%
>= 25 to < 30	32	32%	66	33%	55	27%	122	30%	10	31%	38	34%	29	26%
>= 30	19	19%	32	16%	56	28%	75	18%	8	25%	20	18%	34	30%

8.2.3. Adequacy of the safety database:

The size of safety base met the International Conference on Harmonization (ICH) recommendation for the size of safety data base to characterize the safety profiles for new drugs. Demographic and baseline characteristics, baseline PMH and drug use history among the safety population are typical for the treatment population. The safety population is an adequate representation of the treatment population of subjects with opioid use disorder who are seeking MAT treatment.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Data integrity and submission quality were adequate for this review.

8.3.2. Categorization of Adverse Events

Adverse events were coded using MedDRA version 17.1 for Phase 3 studies and adverse events were coded using MedDRA version 19.1 for the integrated safety datasets. The Applicant provided a table below to summarize the definition of treatment emergent adverse events (TEAE) across the clinical studies. The Applicant's approach is reasonable and appropriate. TEAE definitions for all clinical studies are adequate to characterize the safety profile of RBP-6000.

Table 30 : TEAE definitions for all clinical studies (Applicant's table)

Study	TEAE Definition
Ph3DB: 13-0001	AEs that either commenced following initiation of randomized study treatment or were present prior to the initiation of such, but increased in frequency or severity following initiation of treatment, regardless of causality.
Ph3OL: 13-0003	AEs that either commenced following the first dose of RBP-6000 or were present prior to the first dose of RBP-6000 and increased in frequency or severity following administration of

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

	RBP-6000 regardless of causality.
MAD: 12-0005	<p>AEs that occurred post administration of SUBUTEX SL Tablet.</p> <p>AEs that began prior to a subject receiving SUBUTEX SL Tablet or more than 30 days after the last study subject assessment day were not included.</p> <p>If a partially missing date/time of onset allowed the possibility that an AE may have been a TEAE it was reported as a TEAE.</p> <p>Note that safety presentations were produced for subjects who received SUBUTEX SL Tablet only and both SUBUTEX SL Tablet and RBP-6000</p>
OB: 13-0002	<p>AE that either commenced following exposure to hydromorphone or was present prior to exposure to hydromorphone, but increased in frequency or severity following initiation of RBP-6000 dosing, regardless of causality.</p> <p>Note: AEs occurring post administration of RBP-6000 are summarized separately.</p>
SAD: 11-0020	<p>AEs not present prior to dosing with RBP-6000, or AEs present before study medication that worsened after administration of study medication.</p>
MW: 13-0006	<p>AEs that either commenced following initiation of RBP-6000 or were present prior to the initiation of RBP-6000, but increased in frequency or severity following initiation of treatment, regardless of causality.</p>
FTIH: 10-0011	<p>AEs post administration of RBP-6000.</p>
Safety Summary SAP Presentations	<p>AEs that started or worsened in severity or frequency on or after the first dose of study treatment (RBP-6000 or PBO)</p>

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

8.3.3. **Routine Clinical Tests**

Scheduled central laboratory tests (e.g., hematology, chemistry, urinalysis) were performed every two weeks after screening as showed in Table 9, Table 10 and Table 11 in Phase 3 pivotal study (13-0001). UDS tests were performed weekly during the actual treatment period.

8.4. **Safety Results**

Deaths

There was 1 fatal SAE report (Study 13-0001, gun shot wound) in the RBP-6000 clinical development program as of the NDA data cut-off date. The 39-year-old male subject received a total of 2 injections of RBP-6000 containing 300 mg buprenorphine SC, nineteen days after the second injection, the subject was found deceased from a gunshot wound. Police declared that this was a case of homicide. Accidental injuries are very typical for the patient population with opioid use disorders. Nothing about the case was unusual, and there were no factors suggesting a causal link to the study drug.

8.4.2. **Serious Adverse Events**

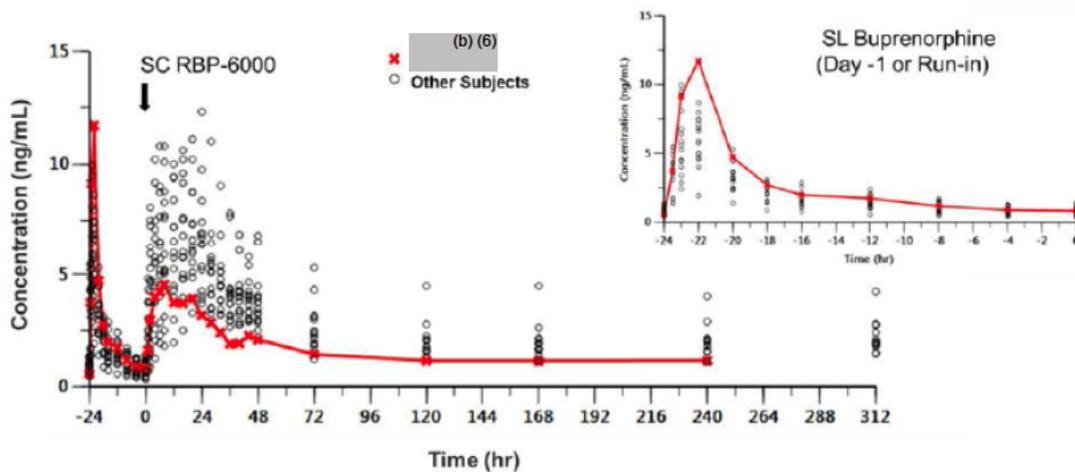
A total of 75 non-fatal SAEs occurred among 65 subjects across 7 studies with 9 SAEs among 6 subjects in the Phase 2 MAD study, 15 SAEs among 13 subjects in the Phase 1 SD studies and a total of 51 SAE cases among 42 subjects in the Phase 3 studies. No Hy's law cases were identified across the studies. No SAEs related to injection site reactions were reported.

Table 32 summarizes SAEs cases in the Phase I and II studies. Causality assessments by the clinical reviewer revealed that the majority of SAEs were not drug related and most were due to pre-existing diseases. In the Phase I molecular weight study (13-0006), one subject developed severe hepatic injury 14 days after the exposure to a single dose of RBP-6000 300 mg PLGH A (Low MW) (Subject ID (b) (6)). The subject required hospitalization and surgical depot removal at day 15; however, hepatitis C was the confounding factor for this case. Upon Agency request, the Applicant submitted the plasma buprenorphine level profile and other relevant medical information. It appears that the plasma buprenorphine level for this subject was not unusually high compared with other subjects in the same cohort group as illustrated in the figure below. The red line and symbols refer to Subject (b) (6). Open circles refer to observed plasma concentrations in other subjects of the low MW group. The Applicant also provided further information that the subject was an IV drug user and was tested positive for hepatitis C at day 17 post exposure. The subject recovered after the RBP-6000 depot removal.

It is likely that both drug and hepatitis C contributed to his severe abnormal liver function and newly-diagnosed hepatitis C played a major role. It is worth noting that this is the only case that required surgical removal of RBP-6000 due to TEAE in the clinical development program. Data for surgical removal of RBP-6000 in case of medical emergency is limited for the clinical development program. There were two SAEs of abnormal liver function tests reported in the Phase I single dose ascending study (11-0020). In these cases, peak ALT/AST level occurred 9-11 weeks post exposure when the plasma buprenorphine level was relatively low and therefore drug contribution was likely to be minimal. One subject (Subject ID (b) (6)) had preexisting hepatitis B and C and another subject (Subject ID (b) (6)) had an elevated alkaline phosphatase level.

Figure 14: Buprenorphine plasma profile for subject (b) (6)

Figure 5 Buprenorphine Plasma Concentration-Time Profile in Subject (b) (6) following Administration of 12 mg Sublingual Buprenorphine (Run-in) and Subsequent Administration of a Single Dose of 300 mg RBP-6000 Formulated with Low Molecular Weight PLGH (Study 13-0006)



Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

Table 36 summarizes SAEs in the Phase 3 studies. A total of 51 non-fatal SAEs occurred among 42 subjects in the pooled Phase 3 studies with 18 SAEs reported in the Phase 3 double-blind, controlled study and 33 SAEs reported in the Phase 3 open-label, uncontrolled study. In the Phase 3 controlled study (13-0001), 3.48% of subjects in the RBP-6000 300/300 mg group reported any SAE compared to 2.0% of the RBP-6000 300/100 group, and 5.0% of the placebo group. In the Phase 3 open-label, uncontrolled study, SAEs were reported in 4.13% of subjects in the RBP-6000 De novo group and in 3.5 % of subjects in the RBP-6000 Roll-over group. No pattern was observed in the SAEs distribution. No Hy's law case was identified in the Phase 3 studies. No SAEs were related to injection site injury. Causality was assessed by reviewing CRF and narrative summaries provided by the Applicant. Most SAEs were not considered to be drug related. SAEs that caused drug discontinuation included gunshot wound, pulmonary embolism, and extradural abscess. The most frequently reported SAEs by body system were infections and infestations, followed by injury, poisoning, procedural complications and psychiatric disorders. Infections, accidental injuries and psychiatric disorder were the most reported medical history at baseline for the patient population. The most frequently reported SAEs (≥ 2) by preferred term included cellulitis, abscess limb, asthma, accidental overdose and gunshot wound.

Over the course of the NDA review, the Applicant provided in vitro assay data showing that when the product was injected in a tube containing dog blood, an immediate clogging was observed (Report FC-FDV-014R). Based on the in vitro tube assay results, it is likely that an occlusion would form due to rapid solidification of the formulation when placed in aqueous fluid. This raised a safety concern about potential consequence if the product was injected improperly via the IV route. In the clinical development program, the product was administered by health care providers in clinical settings; the chance of improper injection is very low. There were no SAEs related to injection injury. To explore further, all SAEs related to thromboembolic disorder were clustered in a group for analyses. There were 5 SAEs related to thromboembolic disorder across studies as summarized in Table 37. These five cases included one case of deep vein thrombosis (DVT), one case of pulmonary embolism (PE), two cases of acute myocardial infarctions and one case of thrombophlebitis. All five cases occurred in the RBP-6000 treatment group; the DVT case was possibly due to chronic venous insufficiency and the two acute MI events occurred in two subjects who were 50-60 years old and carried pre-existing CVD risks such as hypertension, hyperlipidemia, diabetes mellitus, or smoking. Both acute MI events occurred after the first injection of RBP-6000 300 mg and both subjects remained in the study and received additional 5 SC injections of RBP-6000 without further events. The thrombophlebitis case was attributable to IV cocaine use. There were no other alternative explanations for the PE case and the subject was subsequently withdrawn from the study due to PE. This PE case is considered possibly drug related as there was no alternative explanation for his PE. However, the incidence rate of PE (1/1000) in the study population is not significantly higher than that in the general population. So a causal relationship between PE and RBP-6000 cannot be established at this time.

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

Appears this way on original

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 31: SAE summary for Phase 1 and 2 studies

<i>Phase I single dose studies</i>									
<i>Trial</i>	<i>Subject ID</i>	<i>Age (yrs)</i>	<i>Sex</i>	<i>Dose (mg)</i>	<i>Time</i>	<i>Preferred term</i>	<i>W/D</i>	<i>Causality</i>	
<i>RB-US-11-00</i>	(b) (6)	32	M	200	9 weeks	Abnormal liver function test	N/A	Drug-related and hepatitis C, B	
		24	M	100	11 weeks	Abnormal liver function test	N/A	Drug-related and elevated ALP	
		25	F	200	7 weeks	Suicidal ideation	N/A	Pre-existing psychiatric disorder	
		46	M	200	5 weeks	Non-cardiac chest pain	N/A	Not drug-related	
					9 weeks	Suicidal ideation	N/A	Not drug-related	
		57	M	50	50 hours	Non-cardiac chest pain	N/A	Not drug-related	
		58	M	50	17 weeks	Aortic dissection	N/A	Not drug-related	
		36	M	200	5 weeks	Cellulitis	N/A	Not drug-related	
		46	M	200	5 weeks	Non-cardiac chest pain	N/A	Not drug-related	
		33	M	100	18 weeks	Suicidal ideation	N/A	Not drug-related	
<i>RB-US-11-00</i>			19	M	20	4 weeks	Drug withdrawal syndrome	N/A	Not drug-related
<i>RB-US-13-00</i>			31	F	300 PLGH B (H)	10 days	Cellulitis	N/A	Not drug-related
			36	M	300 PLGH B (H)	10 days	MVA/musculoskeleton pain	N/A	Not drug-related
		43	M	300 PLGH A (L)	14 days	Abnormal liver function test	Depot removal	Drug-related and hepatitis C	
<i>Phase II MAD study</i>									
<i>RB-US-12-00</i>	(b) (6)	56	M	200 X 2	27 days after 2ed injection	Deep vein thrombosis (left leg)	W/D	Pre-existing chronic venous insufficiency	
		23	M	200 X 4	16 days after 4th injection	Suicidal ideation/ personality disorder	W/D	Pre-existing psychiatric disorder	
		33	F	100 x 4	3 days after 2ed injection	Lobar pneumonia	No	Not drug-related	
		21	M	100 x 4	23 days after 3rd injection	Asthma exacerbation	No	Not drug-related	
		23	F	100 x 3	8 days after 3rd injection	Bacterial vaginosis /Pelvic inflammatory disease	W/D	Not drug-related	
		35	M	200 x 7	12 days after 7th injection	Thyroid cancer	W/D	Not drug-related	

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 32: SAEs summary for Phase 3 studies

<i>Phase 3 DB study (13-0001)</i>						
	PBO		RBP-6000 300/100 mg		RBP-6000 300/300 mg	
	N=100		N=203		N=201	
Dictionary-Derived Term	N	%	N	%	N	%
Subjects with any SAEs	5	5%	4	2%	7	4.38%
Gun shot wound	2	1.00%
Accidental overdose	1	1.00%
Asthma	1	1.00%	1	0.50%	.	.
Pulmonary embolism	.	.	1	0.50%	.	.
Drug withdrawal syndrome	1	1.00%
Hernia	1	0.50%
Abscess limb	1	0.50%
Extradural abscess	1	1.00%
Acute myocardial infarction	.	.	1	0.50%	.	.
Food poisoning	1	0.50%
Cholelithiasis	1	0.50%
Neuroendocrine carcinoma	.	.	1	0.50%	.	.
Myelomalacia	1	0.50%
Suicidal ideation	1	1.00%
Renal impairment	1	0.50%
Hypotension	1	0.50%

Phase 3 OL study (13-0003)

	RBP-6000 DE NOVO		RBP-6000 ROLL OVER	
	N=412		N=257	
Dictionary-Derived Term	Count	%	Count	%
Subjects with any SAEs	17	4.13%	9	3.50%
Cellulitis	3	0.70%	1	0.40%
Abscess limb	1	0.20%	1	0.40%

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

Appendicitis	.	.	1	0.40%
Escherichia pyelonephritis	.	.	1	0.40%
Localised infection	1	0.20%	.	.
Pneumonia viral	1	0.20%	.	.
Prostatic abscess	1	0.20%	.	.
Staphylococcal bacteraemia	1	0.20%	.	.
Urinary tract infection	1	0.20%	.	.
Accidental overdose	2	0.50%	.	.
Arthropod bite	1	0.20%	.	.
Laceration	1	0.20%	.	.
Multiple fractures	1	0.20%	.	.
Road traffic accident	1	0.20%	.	.
Thermal burn	.	.	1	0.40%
Adjustment disorder with mixed anxiety and depressed mood	.	.	1	0.40%
Bipolar I disorder	1	0.20%	.	.
Major depression	.	.	1	0.40%
Asthma	1	0.20%	1	0.40%
Chronic obstructive pulmonary disease	1	0.20%	.	.
Dizziness	1	0.20%	.	.
Generalised tonic-clonic seizure	.	.	1	0.40%
Myocardial infarction	.	.	1	0.40%
Abdominal pain	1	0.20%	.	.
Gallbladder perforation	1	0.20%	.	.
Hypokalaemia	1	0.20%	.	.
Thrombophlebitis superficial	1	0.20%	.	.

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 33: SAEs summary for thromboembolic disorders

Table 6.8: SAEs summary for thromboembolic disorders									
<i>Trial</i>	<i>Subject ID</i>	<i>Age</i>	<i>Sex</i>	<i>Dose (mg)</i>	<i>Time</i>	<i>Prefered term</i>	<i>W/D</i>	<i>Causality</i>	<i>Alternative explanation</i>
RB-US-12-0005	(b) (6)	56	M	200 X 2	27 days after 2ed injection	Deep vein thrombosis (left leg)	W/D	Not drug related	Hx of chronic venous insufficiency
RB-US-13-0001	(b) (6)	52	M	300 x 2, 100 x4	11 days after 1st injection	Acute myocardial infarction	No	Not drug related	Hypertension, HLD
	(b) (6)	51	M	300 x 2, 100 x3	21 days after 5th injection	Pulmonary embolism	W/D	Possible drug related	
RB-US-13-0003	(b) (6)	59	F	300 x 1, 100 x5	5 days after 1st injection	Acute myocardial infarction	No	Not drug related	Smoking, Hypertenstion, DM
	(b) (6)	28	M	300 x 8	27 days after 3rd injection	Cellulitis/Thrombophlebitis su	No	Not drug related	IV cocaine use

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 35 displays TEAEs leading to drug discontinuation in the Phase 3 studies. In the Phase 3 double-blind, controlled study (13-0001), the percentage of subjects with TEAEs leading to drug discontinuation was higher in the RBP-6000 300/300 mg group (5 %) than the RBP-6000 300/100 mg group (3%), the RBP-6000 300/Flex group (3-4%) and the placebo group (2%). The TEAEs distribution pattern was different between the RBP-6000 300/300 mg group and the other groups. The most common TEAEs leading to drug discontinuation in the RBP-6000 300/300 mg group by preferred term included elevated liver enzymes, sedation, somnolence, injection site ulcers, nausea which are considered drug related and dose dependent. The most common TEAEs leading to drug discontinuation in the RBP-6000 300/100 mg group by preferred term included drug withdrawal syndrome, constipation and rash. TEAEs leading to drug discontinuation in the RBP-6000 300/Flex group included drug withdrawal syndrome, injection site pain, injection site swelling, abnormal liver function tests, sedation, somnolence and constipation.

Table 36 displays TEAEs leading to drug dose reduction in Phase 3 open-label study (13-0003). In the updated full study, 201 (30%) subjects required dose reduction from 300 mg to 100 mg. Among them, 49 (7.3%) subjects required dose reduction from 300 mg to 100 mg due to 61 TEAEs listed in the Table 36. As summarized in Table 36, the most common TEAEs leading to drug dose reductions included abnormal liver function tests, sedation, constipation, nausea, fatigue and headache. Upon Agency request, the Applicant clarified reasons for treatment dose reductions for other 152 (22.7%) subjects as listed below:

140 were due to ending RBP-6000 (110 of these had negative:negative UDS:TLFB at that visit)

68 were PI's decision to reduce dose as subject was doing well

72 were subjects request

12 at PI's discretion:

5 injection site pain reduction/tolerability

3 constipation (captured as AEs in EDC, but not having outcome of dose reduced)

1 LFT (captured as AEs in EDC, but not having outcome of dose reduced)

1 Nausea (AE resolved in EDC before dose reduced)

1 for general health as subjects had multiple health issues

1 unknown

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

I
Table 34: TEAEs leading to drug discontinuation in Phase 3 studies

	Phase 3 DB (13-0001)						Phase 3 Open label (13-0003)								Total	
	PBO		RBP300/100		RBP 300/300		De novo 300/Flex		PBO Roll-over		RBP 100 Roll-over		RBP 300 Roll-over			
<i>Preferred term</i>	N=100		N=203		N=201		N=412		N=32		N=112		N=113		N=916	
Subjects with any TEAEs	2	2%	7	3%	10	5%	12	3%	1	3%	0	0%	3	3%	35	3.82%
Drug withdrawal syndrome	1	1%	2	1%	0	0%	3	1%	0	0%	0	0%	0	0%	6	1%
Aspartate aminotransferase increased	0	0%	0	0%	2	1%	1	<1%	0	0%	0	0%	0	0%	3	<1%
Sedation	0	0%	1	<1%	1	0%	0	0%	0	0%	0	0%	1	1%	3	<1%
Constipation	0	0%	1	<1%	0	0%	1	<1%	0	0%	0	0%	0	0%	2	<1%
Liver function test increased	0	0%	0	0%	1	<1%	1	<1%	0	0%	0	0%	0	0%	2	<1%
Nausea	0	0%	0	0%	1	<1%	1	<1%	0	0%	0	0%	0	0%	2	<1%
Somnolence	0	0%	0	0%	1	<1%	1	<1%	0	0%	0	0%	0	0%	2	<1%
Accidental overdose	0	0%	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	1	<1%
Alanine aminotransferase increased	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Diabetes mellitus	0	0%	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	1	<1%
Extradural abscess	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	<1%
Formication	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Gallbladder perforation	0	0%	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	1	<1%
Gamma-glutamyltransferase increased	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Gun shot wound	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Hepatitis C	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Injection site pain	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	1%	1	<1%
Injection site reaction	0	0%	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	1	<1%
Injection site swelling	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	1%	1	<1%
Injection site ulcer	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Lymphadenitis	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	0	0%	1	<1%
Migraine	0	0%	0	0%	0	0%	0	0%	1	3%	0	0%	0	0%	1	<1%
Neutrophil count decreased	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Pulmonary embolism	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	0	0%	1	<1%

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

Rash	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	0	0%	1	<1%
Vomiting	0	0%	0	0%	1	<1%	0	0%	0	0%	0	0%	0	0%	1	<1%
Weight decreased	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	1%	1	<1%

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 35: TEAEs leading to drug dose reductions in Phase 3 OL, long term study (13-0003)

	De novo 300/Flex		PBO Roll-over		RBP 100 Roll-over		RBP 300 Roll over		Total	
	N=412		N=32		N=112		N=113		N=669	
<i>Preferred term</i>	N	%	N	%	N	%	N	%	N	%
Subjects with any TEAEs	29	7%	4	13%	5	4%	8	7%	46	7%
Alanine aminotransferase increased	5	1%	0	0%	0	0%	1	1%	6	1%
Sedation	2	0%	0	0%	2	2%	3	3%	7	1%
Constipation	4	1%	0	0%	0	0%	1	1%	5	1%
Fatigue	2	0%	1	3%	1	1%	0	0%	4	1%
Aspartate aminotransferase increased	3	1%	0	0%	0	0%	1	1%	4	1%
Nausea	3	1%	0	0%	0	0%	1	1%	4	1%
Gamma-glutamyltransferase increased	1	0%	0	0%	1	1%	0	0%	2	<1%
Headache	3	1%	0	0%	0	0%	0	0%	3	0%
Lethargy	2	0%	0	0%	0	0%	1	1%	3	0%
Somnolence	3	1%	0	0%	0	0%	0	0%	3	0%
Hepatic enzyme increased	1	0%	1	3%	0	0%	0	0%	2	0%
Hepatic function abnormal	2	0%	0	0%	0	0%	0	0%	2	0%
Injection site pain	1	0%	1	3%	0	0%	0	0%	2	0%
Insomnia	2	0%	0	0%	0	0%	0	0%	2	0%
Decreased appetite	0	0%	0	0%	1	1%	0	0%	1	0%
Dizziness	0	0%	0	0%	0	0%	1	1%	1	0%
Erectile dysfunction	0	0%	1	3%	0	0%	0	0%	1	0%
Euphoric mood	1	0%	0	0%	0	0%	0	0%	1	0%
Flushing	0	0%	0	0%	0	0%	1	1%	1	0%
Hypersomnia	1	0%	0	0%	0	0%	0	0%	1	0%
Migraine	1	0%	0	0%	0	0%	0	0%	1	0%
Muscle twitching	0	0%	1	3%	0	0%	0	0%	1	0%
Vomiting	1	0%	0	0%	0	0%	0	0%	1	0%

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

8.4.4. **Significant Adverse Events**

Table 37 and Table 38 summarize severe TEAEs in Phase 3 studies. Percentage of subjects with any severe TEAEs was highest in RBP -6000 300/Flex De novo group (8.5 %) followed by RBP-6000 300/100 mg group (7.38%) and RBP-6000 300/300 mg group (6.47%). Common severe adverse events in RBP-6000 treatment group included headache, abnormal liver enzymes, nausea and constipation.

Table 36: Severe TEAEs summary in Phase 3 study (13-0001) (Percentage occurrence ≥ 2%)

Dictionary-Derived Term	RBP 100 (N=203)		RBP 300 (N=201)		PBO (N=100)	
	Count	%	Count	%	Count	%
Subjects with any severe TEAEs	15	7.39%	13	6.47%	4	4.00%
Drug withdrawal syndrome	1	0.50%	.	.	1	1.00%
Headache	.	.	2	1.00%	.	.
Alanine aminotransferase increased	.	.	1	0.50%	.	.
Anxiety	1	0.50%
Aspartate aminotransferase increased	.	.	1	0.50%	.	.
Blood creatine phosphokinase increased	1	0.50%
Constipation	1	0.50%
Dizziness	1	0.50%
Fatigue	.	.	1	0.50%	.	.
Injection site pruritus	.	.	1	0.50%	.	.
Insomnia	1	1.00%
Nausea	1	0.50%
Somnolence	.	.	1	0.50%	.	.
Tooth abscess	1	0.50%
Toothache	1	0.50%
Vomiting	1	0.50%

Table 37: Severe TEAEs summary in Phase 3 OL study (13-0003) (Percentage occurrence ≥ 2%)

Dictionary-Derived Term	RBP De novo (N=412)		RBP Roll-over (N=257)	
	Count	%	Count	%
Subjects with severe TEAE	35	8.50%	7	2.72%
Constipation	3	0.70%	.	.
Nausea	2	0.50%	.	.
Cellulitis	1	0.20%	1	0.40%
Upper respiratory tract infection	1	0.20%	.	.
Back pain	1	0.20%	.	.
Headache	1	0.20%	.	.
Anxiety	1	0.20%	.	.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The adverse event profile of sublingual buprenorphine has been previously characterized in the safety database for buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets. The safety profile of RBP-6000 is consistent with the established safety profiles of transmucosal buprenorphine products with the exception of injection site reactions.

Table 38 and Table 39 illustrates the common adverse events by body system and preferred term (more than 2%) in the Phase 3 studies. Common adverse events more frequently reported in the RBP-6000 treatment group compared with the placebo group by preferred term included headache, constipation, liver enzymes increased, injection site pruritus, injection site pain, nausea, vomiting, fatigue, somnolence, and sedation. None of these adverse events are unexpected. Common adverse events in the Phase 3 OL study are similar to those in the Phase 3 DB study.

Table 38: Common adverse events in Phase 3 DB study (13-0001) ($\geq 2\%$)

Body system/Preferred term	Actual treatment period		
	PLB	RBP100	RBP300
	Count (%)	Count (%)	Count (%)
Total	N=100	N=203	N=201
Gastrointestinal disorders	12(12%)	51(25.1%)	45(22.4%)
Constipation		19 (9.4)	16 (8)
Nausea	5 (5)	18 (8.9)	16 (8)
Toothache	1 (1)	8 (3.9)	5 (2.5)
Vomiting	4 (4)	19 (9.4)	11 (5.5)
General disorders and administration site conditions	17(17%)	40(19.7%)	49(24.4%)
Fatigue	3 (3)	8 (3.9)	12 (6)
Injection site erythema		9 (4.4)	6 (3)
Injection site pain	3 (3)	10 (4.9)	12 (6)

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Body system/Preferred term	Actual treatment period		
	PLB	RBP100	RBP300
	Count (%)	Count (%)	Count (%)
Injection site pruritus	4 (4)	13 (6.4)	19 (9.5)
Infections and infestations	2(2%)	30(14.8 %)	26(12.9 %)
Nasopharyngitis	1 (1)	11 (5.4)	10 (5)
Tooth abscess		8 (3.9)	5 (2.5)
Upper respiratory tract infection	1 (1)	15 (7.4)	12 (6)
Investigations	2(2%)	21(10.3 %)	19(9.5%)
Alanine aminotransferase increased		2 (1)	10 (5)
Aspartate aminotransferase increased		7 (3.4)	9 (4.5)
Blood creatine phosphokinase increased	1 (1)	11 (5.4)	5 (2.5)
Gamma-glutamyltransferase increased	1 (1)	6 (3)	8 (4)
Nervous system disorders	7(7%)	35(17.2 %)	25(12.4 %)
Dizziness	2 (2)	5 (2.5)	3 (1.5)
Headache	6 (6)	19 (9.4)	17 (8.5)
Sedation		7 (3.4)	3 (1.5)
Somnolence		10 (4.9)	4 (2)

Table 39: Common adverse events in Phase 3 OL study (13-0003) ($\geq 2\%$)

	Actual Treatment for Period 01		
	RBP-6000 DE NOVO	RBP-6000 ROLL-OVER	Total
	Count (%)	Count (%)	Count (%)
Total	N=412	N=257	N=669

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

	Actual Treatment for Period 01		
	RBP-6000 DE NOVO	RBP-6000 ROLL-OVER	Total
	Count (%)	Count (%)	Count (%)
Gastrointestinal disorders	94(22.8%)	26(10.1%)	120(17.9%)
Constipation	48 (11.7)	9 (3.5)	57 (8.5)
Nausea	34 (8.3)	11 (4.3)	45 (6.7)
Toothache	15 (3.6)	5 (1.9)	20 (3)
Vomiting	15 (3.6)	7 (2.7)	22 (3.3)
General disorders and administration site conditions	67(16.3%)	21(8.2%)	88(13.2%)
Fatigue	19 (4.6)	3 (1.2)	22 (3.3)
Injection site erythema	21 (5.1)	5 (1.9)	26 (3.9)
Injection site pain	33 (8)	8 (3.1)	41 (6.1)
Injection site pruritus	17 (4.1)	9 (3.5)	26 (3.9)
Infections and infestations	57(13.8%)	20(7.8%)	77(11.5%)
Cellulitis	10 (2.4)	4 (1.6)	14 (2.1)
Nasopharyngitis	24 (5.8)	4 (1.6)	28 (4.2)
Upper respiratory tract infection	18 (4.4)	5 (1.9)	23 (3.4)
Urinary tract infection	12 (2.9)	8 (3.1)	20 (3)
Investigations	19(4.6%)	13(5.1%)	32(4.8%)
Alanine aminotransferase increased	10 (2.4)	5 (1.9)	15 (2.2)
Aspartate aminotransferase increased	10 (2.4)	5 (1.9)	15 (2.2)
Gamma-glutamyltransferase increased	10 (2.4)	12 (4.7)	22 (3.3)
Musculoskeletal and connective tissue disorders	24(5.8%)	6(2.3%)	30(4.5%)
Arthralgia	12 (2.9)	3 (1.2)	15 (2.2)
Back pain	15 (3.6)	3 (1.2)	18 (2.7)

	Actual Treatment for Period 01		
	RBP-6000 DE NOVO	RBP-6000 ROLL-OVER	Total
	Count (%)	Count (%)	Count (%)
Nervous system disorders	40(9.7%)	5(1.9%)	45(6.7%)
Headache	30 (7.3)	3 (1.2)	33 (4.9)
Somnolence	12 (2.9)	2 (0.8)	14 (2.1)
Psychiatric disorders	38(9.2%)	17(6.6%)	55(8.2%)
Anxiety	13 (3.2)	7 (2.7)	20 (3)
Insomnia	26 (6.3)	11 (4.3)	37 (5.5)
Skin and subcutaneous tissue disorders	10(2.4%)	5(1.9%)	15(2.2%)
Rash	10 (2.4)	5 (1.9)	15 (2.2)

8.4.6. Laboratory Findings

In general, the only notable effects on laboratory values were, as expected, elevations in hepatic enzymes. This is a known effect of buprenorphine.

Table 40 and Table 41 displays subjects with liver function test values greater than the upper limit of normal post-baseline in the Phase 3 double-blind study (13-0001) and Phase 3 open-label study (13-0003), respectively. Overall, a higher percentage of subjects in the RBP-6000 treatment groups had LFT values (ALT and AST) greater than 2 X ULN post-baseline than in the placebo group. Furthermore, percentage of subjects with LFT values greater than 3 x ULN was higher in the high dose regimens RBP-6000 300/300 mg (ALT: 12.44%, AST: 11.44%) compared with low dose regimen RBP-6000 300/100 mg (ALT: 5.42%, AST: 7.88%). It is unclear if the percentage of abnormal LFT values in the RBP-6000 treatment group is higher than would be expected with Suboxone treatment.

Table 40: Subjects with LFT values greater than upper limit of normal in Phase 3 DB study (13-0001)

Liver Lab Test	Placebo N = 100			RBP-6000 100 mg N = 203			RBP-6000 300 mg N = 201		
	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
ALT ≥ ULN									
2x ULN	20	12	12.00	100	35	17.24	151	36	17.91
3x ULN	8	4	4.00	34	11	5.42	72	25	12.44
5x ULN	5	2	2.00	17	5	2.46	19	7	3.48
10x ULN	2	1	1.00	8	2	0.99	9	3	1.49
20x ULN	1	1	1.00	2	1	0.49	0	0	0.00
AST ≥ ULN									
2x ULN	8	6	6.00	108	25	12.32	155	33	16.42
3x ULN	3	1	1.00	50	16	7.88	56	23	11.44
5x ULN	3	1	1.00	13	6	2.96	17	8	3.98
10x ULN	2	1	1.00	2	1	0.49	5	4	1.99
20x ULN	1	1	1.00	1	1	0.49	0	0	0.00
ALP ≥ ULN									
2x ULN	2	2	2.00	15	3	1.48	2	1	0.50
3x ULN	0	0	0.00	14	2	0.99	0	0	0.00
5x ULN	0	0	0.00	1	1	0.49	0	0	0.00
10x ULN	0	0	0.00	0	0	0.00	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00	0	0	0.00
TB ≥ ULN									
1.5x ULN	1	1	1.00	2	2	0.99	5	2	1.00
2x ULN	0	0	0.00	1	1	0.49	1	1	0.50
3x ULN	0	0	0.00	0	0	0.00	0	0	0.00

Table 41: : Subjects with LFT values greater than upper limit of normal in Phase 3 open-label study (13-0003)

Liver Lab Test	RBP-6000 DE Novo N = 412			RBP-6000 Roll-Over N = 257		
	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
ALT ≥ ULN						
2x ULN	336	84	20.39	169	48	18.68

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

3x ULN	173	51	12.38	70	21	8.17
5x ULN	70	29	7.04	26	9	3.50
10x ULN	20	12	2.91	6	1	0.39
20x ULN	4	2	0.49	0	0	0.00
AST ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	297	84	20.39	181	44	17.12
3x ULN	136	45	10.92	94	25	9.73
5x ULN	59	21	5.10	39	13	5.06
10x ULN	19	11	2.67	5	2	0.78
20x ULN	2	2	0.49	0	0	0.00
ALP ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	38	10	2.43	19	5	1.95
3x ULN	12	3	0.73	16	3	1.17
5x ULN	2	1	0.24	2	1	0.39
10x ULN	0	0	0.00	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00
TB ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
1.5x ULN	25	11	2.67	3	3	1.17
2x ULN	11	6	1.46	0	0	0.00
3x ULN	3	1	0.24	0	0	0.00

8.4.7. Vital Signs

In the Ph3DB study, mean values for systolic and diastolic BP, pulse oximetry, pulse rate, respiratory rate and oral temperature were generally within the reference ranges for each parameter and were similar across all 3 treatment groups. Mean values for these parameters were also generally within the reference ranges for subjects in the Ph3OL study.

8.4.8. Electrocardiograms (ECGs)

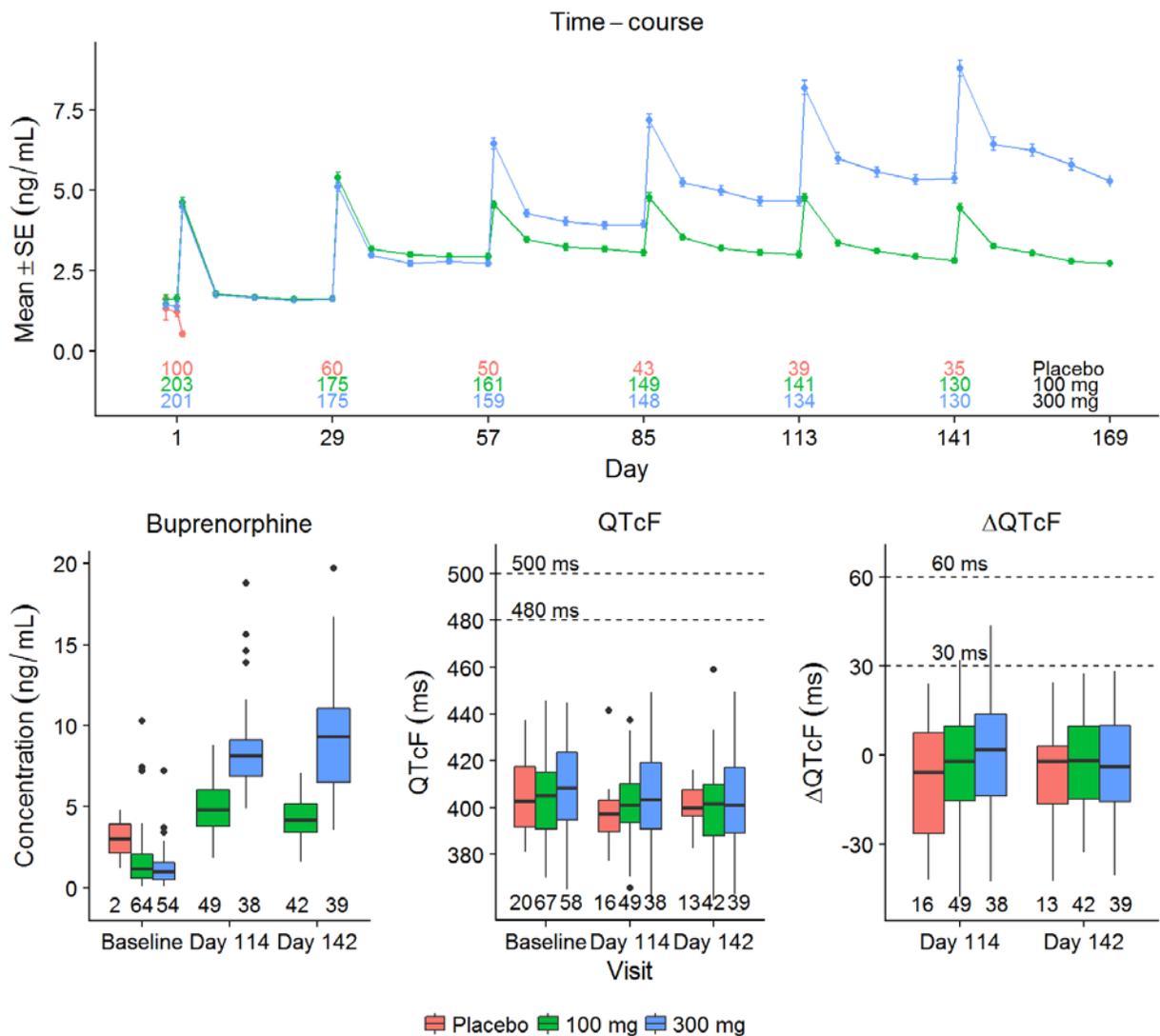
An EKG data base (over 11,900 EKG in over 1100 subjects with OUD), including time-matched buprenorphine samples was submitted in this NDA. The data were reviewed by the CDER QT-IRT team.

8.4.9. QT

A signal for QT prolongation has been identified in a study of transdermal buprenorphine used for analgesia. The extent of prolongation noted was considered to meet the threshold for regulatory concern, a value which is used to determine whether or not the effect of a drug on

the QT/QTc interval in target patient populations should be studied intensively during later stages of drug development. The potential for doses of buprenorphine used for the treatment of opioid dependence to prolong the QT interval has not yet been evaluated in formal QT studies. An EKG data base (over 11,900 EKG in over 1100 subjects with OUD), including time-matched buprenorphine samples was submitted in this NDA. The data were review by the CDER QT-IRT team. They concluded that the observed QTc prolongation appears to saturate around ~10 ms despite of high exposure level of RBP-6000 (Figure 15).

Figure 15: QT effects of RBP-6000 (Generated by QT-IRT team)



Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

8.4.10. **Immunogenicity**

There are no specific data on the effect of immunogenicity on safety, efficacy, and/or clinical pharmacology and pharmacokinetics for RBP-6000.

8.5. **Analysis of Submission-Specific Safety Issues**

Safety topic of special interest included injection site reactions, hepatic effects, CNS depression, respiratory depression, cardiac conduction effects, and orthostatic hypotension. Acute pancreatitis was included as a topic of special interest due to a nonclinical safety finding of pancreatic acinar cell apoptosis.

8.5.1. **Injection site reactions**

To better understand local injection tolerability, TEAEs with injection site injuries in pooled Phase 3 studies were categorized by actions on the study treatment and AE severity separately. Table 43 shows that most of the injection site injuries were mild to moderate except one subject reported severe injection site pruritus in the RBP-6000 300/300 mg group. Overall, a higher percentage of TEAEs related to injection site injuries were reported in the RBP-6000 300/300 mg group (18.4%) than the RBP-6000 300/100 mg group (13.8%), RBP-6000 300/Flex group (5-14%) and placebo group (9%). Table 43 displays TEAEs with injection site injuries by actions on the study treatment. TEAEs related to injection site injuries leading to drug discontinuation included 1 injection site ulcer in the RBP-6000 300/300 mg group, and 1 injection site reaction in the RBP-6000 300/Flex group. A total of two subjects required drug dose reduction in the RBP-6000 300/Flex group due to injection site pain. The safety database of RBP-6000 reveals that local injection tolerability of RBP-6000 is acceptable. However, the safety database of RBP-6000 also reveals that the high dose regimen RBP-6000 300/300 mg was less tolerated compared with RBP-6000 300/Flex as evidenced by the higher percentage of TEAEs related to injection site injuries in RBP-6000 300/300 mg group.

Table 42: TEAEs related to injection site reactions by severity in Phase 3 studies

		Phase III DB (13-0001)						Phase III Open label (13-0003)							
		PB O		RBP300/100		RBP 300/300		e novo 300/Fle		PBO Roll- over		0 Roll-over 30		300 Roll over 300/	
		N=100		N=203		N=201		N=412		N=32		N=112		N=113	
<i>AE Severity</i>	<i>Preferred term</i>	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	Any TEAEs	9	9%	28	13.8%	37	18.4%	58	14.0%	2	6.25%	13	11.6%	6	5.30%
MILD	Injection site bruising	0	0%	1	0.9%	2	1%	1	0%	0	0%	0	0%	0	0%
MILD	Injection site discomfort	0	0%	1	0%	0	0%	2	.4%	0	0%	0	0%	0	0%
MILD	Injection site erythema	0	0%	7	3.4%	3	1.4%	16	3.8%	0	0%	4	3.5%	1	.8%
MILD	Injection site haematoma	0	0%	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%
MILD	Injection site infection	0	0%	0	0%	0	0%	1	0.2%	0	0%	0	0%	0	0%
MILD	Injection site inflammation	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MILD	Injection site mass	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
MILD	Injection site nodule	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
MILD	Injection site pain	1	1%	7	3%	10	4.9%	20	4.8%	1	3%	2	1.7%	2	1.7%
MILD	Injection site pruritus	3	3%	7	3.4%	11	5%	14	3%	1	3%	6	5%	2	1.7%
MILD	Injection site swelling	0	0%	1	0%	1	0%	1	0%	0	0%	1	0.8%	1	.8%
MILD	Injection site warmth	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Injection site cellulitis	0	0%	0	0%	0	0%	1	0.2%	0	0%	0	0%	0	0%
MODERATE	Injection site dermatitis	0	0%	0	0%	0	0%	0	0%	0	0%	1	.8%	0	0%
MODERATE	Injection site discomfort	0	0%	0	0%	1	0%	1	0%	0	0%	0	0%	0	0%
MODERATE	Injection site erythema	0	0%	2	0.9%	3	1%	4	0.9%	0	0%	0	0%	0	0%
MODERATE	Injection site induration	0	0%	1	0%	1	0%	1	0%	0	0%	0	0%	0	0%
MODERATE	Injection site oedema	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Injection site infection	1	1%	0	0%	1	.4%	1	0.2%	0	0%	0	0%	0	0%
MODERATE	Injection site pain	2	2%	3	1%	2	0.9%	9	2.1%	1	3%	0	0%	2	1.7%
MODERATE	Injection site pruritus	1	1%	4	1.9%	7	3%	3	.7%	0	0%	0	0%	0	0%
MODERATE	Injection site rash	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Injection site reaction	0	0%	0	0%	0	0%	1	0%	0	0%	3	2.6%	0	0%

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

MODERATE	Injection site swelling	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Injection site ulcer	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
SEVERE	Injection site pruritus	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
SEVERE	Injection site cellulitis	0	0%	0	0%	0	0%	1	0.2%	0	0%	0	0%	0	0%

Table 43: TEAEs related to injection site reactions by actions on study drugs

		Phase 3 DB study (13-0001)						Phase 3 OL study (13-0003)	
		PBO		RBP-6000 300/100 mg		RBP-6000 300/300 mg		RBP-6000 300/Flex	
		N=100		N=203		N=201		N=444	
<i>Actions on study treatment</i>	<i>Preferred term</i>	N	%	N	%	N	%	N	%
DOSE REDUCED	Injection site pain	0	0%	0	0%	0	0%	1	0%
DRUG WITHDRAWN	Injection site reaction	0	0%	0	0%	0	0%	1	0%
DRUG WITHDRAWN	Injection site pain	0	0%	0	0%	1	0%	0	0%
DRUG WITHDRAWN	Injection site swelling	0	0%	0	0%	1	0%	0	0%
DRUG WITHDRAWN	Injection site ulcer	0	0%	0	0%	1	0%	0	0%

8.5.2. Hepatic effects

Buprenorphine has been associated with hepatitis and other hepatic events. The Warnings and Precautions section of current labeling for sublingual buprenorphine (as Suboxone) includes safety labeling regarding hepatitis and hepatic events as follows:

5.8 Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in amelioration of acute hepatitis in some cases; however, in other cases no dose reduction was necessary. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment, are recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, SUBOXONE sublingual film may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

No Hy's law case was identified in the clinical development program. As described in SAE Section , a total of 3 SAEs of hepatic injuries were reported in the pooled Phase 1 studies after single dose exposure at 100 mg, 200 mg and 300 mg (Low molecular weight). One subject had newly diagnosed hepatitis C after the drug exposure, one subject had preexisting hepatitis C and B, and one subject had elevated Alkaline Phosphatase level. Therefore, all these three cases do not meet the Hy's law criteria. This is consistent with the baseline medical history as approximately 10% of patients reported a history of hepatitis C. Safety assessment focused on examining whether hepatic effects are dose-dependent as RBP-6000 has a higher exposure level (>2 ng /ml) compared with approved transmucosal buprenorphine products.

Table 44 displays reported TEAEs related to hepatic events by actions on study treatment in the Phase 3 studies. In the Phase 3 DB study, a few cases of TEAEs of hepatic injuries leading to drug discontinuation occurred in the RBP 6000 300/300 mg group, but not in the RBP-6000 300/100 mg group and the placebo group. TEAEs of hepatic injuries leading to drug reduction and drug discontinuation were also reported in the *de novo* 300/Flex group.

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 44: Reported TEAEs related to hepatic injuries by action on study treatment in Phase 3 studies

		Phase 3 DB (13-0001)						Phase 3 Open label (13-0003)							
		PBO		RBP300/100		RBP 300/300		nov 300/Fle		PBO Roll-over		0 Roll-over 30		0 Roll over 30	
		N=100		N=203		N=201		N=412		N=32		N=112		N=113	
<i>Actions on study drug</i>	<i>Preferred term</i>	N	%	N	%	N	%	N	%	N	%	N	%	N	%
DOSE REDUCED	Alanine aminotransferase increased	0	0%	0	0%	0	0%	5	1%	0	0%	1	1%	1	1%
DOSE REDUCED	Aspartate aminotransferase increased	0	0%	0	0%	0	0%	3	1%	0	0%	0	0%	1	1%
DOSE REDUCED	Gamma-glutamyltransferase increased	0	0%	0	0%	0	0%	1	0%	0	0%	2	2%	0	0%
DOSE REDUCED	Hepatic enzyme increased	0	0%	0	0%	0	0%	1	0%	1	3%	0	0%	0	0%
DOSE REDUCED	Hepatic function abnormal	0	0%	0	0%	0	0%	2	0%	0	0%	0	0%	0	0%
DRUG WITHDRAWN	Alanine aminotransferase increased	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%
DRUG WITHDRAWN	Aspartate aminotransferase increased	0	0%	0	0%	2	1%	1	0%	0	0%	0	0%	0	0%
DRUG WITHDRAWN	Gallbladder perforation	0	0%	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%
DRUG WITHDRAWN	Gamma-glutamyltransferase increased	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%
DRUG WITHDRAWN	Liver function test increased	0	0%	0	0%	1	0%	1	0%	0	0%	0	0%	0	0%

Table 45: Reported TEAEs related to hepatic injuries by severity in Phase 3 studies

AE Severity	Preferred term	Phase 3 DB (13-0001)						Phase 3 Open label (13-0003)							
		PBO		RBP300/100 mg		RBP 300/300		De novo 300/Flex		PBO Roll-over 300/F		100 Roll-over 300/F		RBP 300 Roll over 300/Flex	
		N=100	N=203	N=201	N=412	N=32	N=112	N=113							
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
	Subjects with any TEAEs	1	1.00%	14	6.90%	15	7.50%	39	9.46%	1	3.00%	9	7.00%	7	6.19%
MILD	Alanine aminotransferase increased	0	0.00%	1	0.49%	5	2.49%	4	0.97%	0	0.00%	0	0.00%	3	4.42%
MILD	Aspartate aminotransferase increased	0	0.00%	4	1.97%	4	1.99%	3	0.73%	0	0.00%	1	0.89%	3	3.54%
MILD	Bilirubin conjugated increased	0	0.00%	0	0.00%	1	0.50%	0	0.00%	0	0.00%	0	0.00%	0	0.88%
MILD	Blood bilirubin increased	0	0.00%	1	0.49%	1	0.50%	3	0.73%	0	0.00%	0	0.00%	0	0.88%
MILD	Hepatic enzyme increased	0	0.00%	1	0.49%	0	0.00%	1	0.24%	0	0.00%	0	0.00%	0	0.00%
MILD	Hepatic function abnormal	0	0.00%	0	0.00%	0	0.00%	1	0.24%	0	0.00%	0	0.00%	0	0.00%
MILD	Liver function test increased	0	0.00%	0	0.00%	2	1.00%	4	0.97%	0	0.00%	0	0.00%	0	1.77%
MODERATE	Alanine aminotransferase increased	0	0.00%	1	0.49%	4	1.99%	7	1.70%	0	0.00%	2	1.79%	3	3.54%
MODERATE	Aspartate aminotransferase increased	0	0.00%	3	1.48%	4	1.99%	7	1.70%	0	0.00%	1	0.89%	3	3.54%
MODERATE	Biliary dilatation	0	0.00%	0	0.00%	1	0.50%	0	0.00%	0	0.00%	0	0.00%	0	0.88%
MODERATE	Bilirubin conjugated increased	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	0.89%	0	0.00%
MODERATE	Blood alkaline phosphatase increased	1	1.00%	1	0.49%	0	0.00%	1	0.24%	0	0.00%	1	0.89%	0	0.00%
MODERATE	Blood bilirubin increased	0	0.00%	0	0.00%	0	0.00%	1	0.24%	0	0.00%	1	0.89%	0	0.00%
MODERATE	Cholelithiasis	0	0.00%	0	0.00%	1	0.50%	1	0.24%	0	0.00%	0	0.00%	0	0.88%
MODERATE	Hepatic function abnormal	0	0.00%	0	0.00%	0	0.00%	5	1.21%	0	0.00%	0	0.00%	0	0.00%
MODERATE	Liver function test increased	0	0.00%	3	1.48%	0	0.00%	2	0.49%	0	0.00%	1	0.89%	0	0.00%
MODERATE	Transaminases increased	0	0.00%	0	0.00%	0	0.00%	1	0.24%	0	0.00%	0	0.00%	0	0.00%
SEVERE	Alanine aminotransferase increased	0	0.00%	0	0.00%	1	0.50%	0	0.00%	0	0.00%	0	0.00%	0	0.88%
SEVERE	Aspartate aminotransferase increased	0	0.00%	0	0.00%	1	0.50%	0	0.00%	0	0.00%	0	0.00%	0	0.88%
SEVERE	Blood bilirubin increased	0	0.00%	0	0.00%	0	0.00%	1	0.24%	0	0.00%	0	0.00%	0	0.00%
SEVERE	Hepatic enzyme increased	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	3.13%	0	0.00%	0	0.00%
SEVERE	Hepatic function abnormal	0	0.00%	0	0.00%	0	0.00%	1	0.24%	0	0.00%	0	0.00%	0	0.00%
SEVERE	Jaundice	0	0.00%	0	0.00%	0	0.00%	1	0.24%	0	0.00%	0	0.00%	0	0.00%
SEVERE	Liver function test increased	0	0.00%	0	0.00%	1	0.50%	0	0.00%	0	0.00%	0	0.00%	0	0.88%

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

Table 45 displays TEAEs of hepatic injuries by severity. A slightly higher percentage of TEAEs of hepatic injuries were reported in the RBP-6000 300/300 mg group (7.5%) , RBP-6000 300/100 mg group (6.9%) and RBP -6000 300/flex group (3-9 %) compared with the placebo group(1%). A total of 3 severe TEAEs of hepatic injuries were reported in the RBP-6000 300/300 mg group and 3 severe TEAEs of hepatic injuries were reported in the de novo 300/flex group. In summary, the safety database reveals that hepatic injuries were buprenorphine dose-dependent as evidenced by earlier drop outs due to hepatic injuries in the RBP-6000 300/300 mg group and more subjects requiring dose reduction in the de novo 300/300 group due to hepatic injuries.

8.5.3. CNS depression

A Customized MedDRA Query (CMQ) regarding CNS depression was performed in pooled Phase 3 studies. As shown in Table 46, in the Ph3DB study, TEAEs potentially associated with CNS depression were observed at a higher percentage in the RBP-6000 treatment group 300/100 mg group (11.8%) than in the 300/300 mg group (7.0%) compared with placebo group (4.0%). In the Ph3OL study, the percentages of subjects with reports of these TEAEs ranged from 7% to 8 % across subject groups. In the Ph3DB study, none of the TEAEs potentially associated with CNS depression were serious, except for accidental overdose in 1 subject (Subject (b) (6)) in the PBO group. Three subjects discontinued study treatment due to events potentially pertaining to CNS depression: 2 subjects with sedation (1 each in the 300/100 mg and 300/300 mg groups) and 1 subject with somnolence in the 300/300 mg group.

In the Ph3OL study, 5 subjects had SAEs potentially associated with CNS depression (accidental overdose [de novo Subjects (b) (6) and (b) (6)]; road traffic accident [de novo Subject (b) (6)]; dizziness [de novo Subject (b) (6)]; and generalized tonic-clonic seizure [roll-over Subject (b) (6)]). Two subjects in the de novo 300 mg group discontinued study treatment due to events potentially pertaining to CNS depression: accidental overdose (Subject (b) (6)) and somnolence (Subject (b) (6)). One subject in the roll-over group discontinued study treatment due to sedation (Subject (b) (6)).

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 46: TEAEs related to CNS depression in Phase 3 studies

Preferred Term	Phase III DB (13-0001)						Phase III Open label (13-0003)							
	PBO		RBP300/100 mg		RBP 300/300		De novo 300/Flex		PBO Roll-over 300/Flex		RBP 100 Roll-over 300/Flex		RBP 300 Roll over 300/Flex	
	N=100		N=203		N=201		N=412		N=32		N=112		N=113	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Subjects with any TEAEs related to CNS	4	4%	24	12%	14	7%	30	7%	3	6%	7	6%	9	8%
Somnolence	1	1%	15	7%	5	2%	12	3%	2	6%	5	4%	1	1%
Sedation	0	0%	8	4%	4	2%	4	1%	0	0%	6	5%	6	5%
Dizziness	2	2%	6	3%	3	1%	3	1%	1	3%	1	1%	3	3%
Lethargy	1	1%	1	0%	3	1%	3	1%	1	3%	1	1%	1	1%
Road traffic accident	0	0%	3	1%	1	0%	4	1%	0	0%	0	0%	3	3%
Vision blurred	0	0%	2	1%	0	0%	2	0%	0	0%	0	0%	0	0%
Loss of consciousness	1	1%	0	0%	0	0%	2	0%	0	0%	0	0%	0	0%
Sluggishness	0	0%	0	0%	1	0%	0	0%	1	3%	0	0%	0	0%
Syncope	0	0%	0	0%	0	0%	2	0%	0	0%	0	0%	0	0%
Cognitive disorder	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
Dizziness postural	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Generalised tonic-clonic seizure	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	1%
Seizure	0	0%	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

8.5.4. **Opioid Withdrawal Signs and Symptoms**

Applicant performed a custom MedDRA query (CMQ) for TEAEs related to opioid withdrawal signs and symptoms. TEAEs potentially associated with opioid withdrawal signs and symptoms were observed for similar percentages of subjects across treatment groups (300/100 mg 35.0% and 300/300 mg 29.9% vs PBO 36.0%). In the Ph3OL study, the percentage of subjects with at least 1 TEAE potentially associated with opioid withdrawal signs and symptoms ranged from 15.0% to 27.9% across subject groups.

As shown in the table below, the specific symptoms that occurred most frequently in the RBP-6000 treated groups were nausea/vomiting and insomnia, which are not specific for drug withdrawal.

Table 47: TEAEs related to opioid withdrawal signs and symptoms in Phase 3 studies (Applicant’s table)

Preferred Term	13-0001 (Phase 3 DB)			13-0003 (Phase 3 OL)			All Phase 3 (13-0001 & 13-0003)	
				Roll-over				De novo
	RBP-6000 300/100 (N = 203) n (%)	RBP-6000 300/300 (N = 201) n (%)	PBO (N = 100) n (%)	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 (%)	Total RBP-6000 (N=848) n (%)
Any TEAEs	71 (35.0)	60 (29.9)	36 (36.0)	23 (20.5)	17 (15.0)	8 (25.0)	115 (27.9)	273 (32.2)
Nausea	18 (8.9)	16 (8.0)	5 (5.0)	4 (3.6)	4 (3.5)	3 (9.4)	35 (8.5)	80 (9.4)
Insomnia	13 (6.4)	17 (8.5)	11 (11.0)	10 (8.9)	1 (0.9)	0	27 (6.6)	65 (7.7)
Vomiting	19 (9.4)	11 (5.5)	4 (4.0)	3 (2.7)	3 (2.7)	1 (3.1)	18 (4.4)	54 (6.4)
Anxiety	10 (4.9)	8 (4.0)	5 (5.0)	4 (3.6)	3 (2.7)	1 (3.1)	13 (3.2)	37 (4.4)
Drug withdrawal syndrome	9 (4.4)	7 (3.5)	6 (6.0)	1 (0.9)	0	0	10 (2.4)	26 (3.1)
Arthralgia	4 (2.0)	3 (1.5)	3 (3.0)	2 (1.8)	1 (0.9)	0	12 (2.9)	22 (2.6)
Diarrhoea	5 (2.5)	5 (2.5)	5 (5.0)	0	0	0	7 (1.7)	17 (2.0)
Dizziness	5 (2.5)	3 (1.5)	2 (2.0)	1 (0.9)	3 (2.7)	1 (3.1)	3 (0.7)	16 (1.9)
Hyperhidrosis	4 (2.0)	4 (2.0)	0	1 (0.9)	0	0	7 (1.7)	16 (1.9)
Decreased appetite	1 (0.5)	4 (2.0)	3 (3.0)	1 (0.9)	0	2 (6.3)	6 (1.5)	14 (1.7)
Hypertension	3 (1.5)	2 (1.0)	0	2 (1.8)	2 (1.8)	0	5 (1.2)	13 (1.5)
Muscle spasms	0	3 (1.5)	1 (1.0)	2 (1.8)	1 (0.9)	1 (3.1)	6 (1.5)	13 (1.5)
Pruritus	4 (2.0)	3 (1.5)	0	0	0	0	3 (0.7)	10 (1.2)
Depression	2 (1.0)	0	4 (4.0)	1 (0.9)	1 (0.9)	0	5 (1.2)	9 (1.1)
Myalgia	0	0	1 (1.0)	0	1 (0.9)	0	8 (1.9)	9 (1.1)

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

8.5.5. **Reparatory depression**

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

8.5.6. **Orthostatic hypotension**

Applicant performed a CMQ for TEAEs related to orthostatic hypotension. In the Ph3DB study, TEAEs potentially associated with orthostatic hypotension were slightly higher in the 300/100 mg group (3.4%) compared with the 300/300 mg group (2.5%) and placebo group (2.0%). In the Ph3OL study, the percentage of subjects with TEAEs potentially associated with orthostatic hypotension ranged from 0.9% to 3.1% across subject groups. In the Ph3DB study, 1 of the TEAEs events potentially associated with orthostatic hypotension was an SAE of hypotension associated with renal impairment in a subject in the 300/300 mg group. His SAE of hypotension was attributed to anti-hypertension medications.

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 48: TEAEs related to orthostatic hypotension in Phase 3 studies (Applicant’s table)

Preferred Term	13-0001 (Phase 3 DB)			13-0003 (Phase 3 OL)			All Phase 3 (13-0001 & 13-0003)	
				Roll-over				De novo
	RBP-6000 300/100 (N = 203) n (%)	RBP-6000 300/300 (N = 201) n (%)	PBO (N = 100) n (%)	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 (%)	Total RBP-6000 (N=848) n (%)
Any TEAEs	7 (3.4)	5 (2.5)	2 (2.0)	1 (0.9)	3 (2.7)	1 (3.1)	6 (1.5)	23 (2.7)
Dizziness	5 (2.5)	3 (1.5)	2 (2.0)	1 (0.9)	3 (2.7)	1 (3.1)	3 (0.7)	16 (1.9)
Vision blurred	2 (1.0)	0	0	0	0	0	1 (0.2)	3 (0.4)
Hypotension	0	2 (1.0)	0	0	0	0	0	2 (0.2)
Syncope	0	0	0	0	0	0	2 (0.5)	2 (0.2)
Dizziness postural	1 (0.5)	0	0	0	0	0	0	1 (0.1)

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

8.5.7. **Acute pancreatitis**

A standardized MedDRA Query (SMQ) regarding pancreatitis disorder was performed in pooled Phase 3 studies and Table 49 displays TEAEs related to pancreatitis in Phase 3 studies. Although nonspecific symptoms such as nausea, vomiting were frequently reported in both placebo group and RBP-6000 treatment group, very few cases reported pancreatic enzymes increased (amylase, trypsin and lipase). TEAEs related to pancreatic enzymes increased were evenly distributed between placebo group and RBP-6000 treatment group. The safety database of RBP-6000 did not reveal that acute pancreatitis is a new safety signal.

Table 49: TEAEs related to acute pancreatitis in Phase 3 studies

Phase 3 DB study (13-0001)						
AEDECOD	PBO (N=100)		RBP 100 MG (N=203)		RBP 300 (N=201)	
Preferred term	N	%	N	%	N	%
Subjects with any TEAEs	14	14%	45	22%	31	15%
Abdominal distension	0	0%	1	0%	0	0%
Abdominal pain	3	3%	2	1%	2	1%
Abdominal pain upper	1	1%	5	2%	3	1%
Abdominal tenderness	0	0%	1	0%	0	0%
Amylase increased	2	2%	2	1%	0	0%
Blood bilirubin increased	0	0%	1	0%	1	0%
Blood trypsin increased	0	0%	2	1%	0	0%
Lipase increased	1	1%	3	1%	1	0%
Nausea	7	7%	20	10%	19	9%
Pancreatitis	0	0%	0	0%	1	0%
Vomiting	9	9%	25	12%	18	9%
Phase 3 OL study (13-0003)						
AEDECOD	De novo (N=412)		Roll over (N=257)			
Preferred term	N	%	N	%		
Subjects with any TEAEs	55	13.40%	26	10.11%		
Abdominal distension	1	0%	1	0%		
Abdominal pain	6	1%	1	0%		
Abdominal pain upper	1	0%	2	1%		
Amylase increased	1	0%	2	1%		
Blood bilirubin increased	5	1%	1	0%		
Blood trypsin increased	0	0%	1	0%		
Jaundice	1	0%	0	0%		
Lipase increased	2	0%	2	1%		
Nausea	40	10%	14	5%		
Pancreatic enzymes increased	1	0%	0	0%		
Vomiting	22	5%	9	4%		

8.5.8. Cardiac disorder

A Customized MedDRA Query (CMQ) regarding cardiac disorder was performed in pooled Phase 3 studies and Table 54 displays TEAEs of cardiac disorder including cardiac arrhythmia and reported abnormal EKG findings in Phase 3 studies. Overall, TEAEs of cardiac disorder were rarely reported and evenly distributed across groups (Table 50). A few cases of mild to moderate QT prolongation were reported in the RBP-6000 treatment group which were

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

considered non-clinically significant. These findings are consistent with the EKG findings from QT-IRT team.

As described earlier in SAE Section, one SAE of acute myocardial infarction was reported in the RBP 300/100 group at the early stage of the treatment, which was attributed to preexisting cardiac risks and the subject continued to receive the treatment after the event. The other SAE of acute myocardial infarction was reported in a subject who rolled over from the RBP-6000 group. After the event, the subject continued to receive drug treatment and completed the trial. Both SAEs of acute myocardial infarction were considered not drug related.

Table 50: TEAEs related to cardiac disorder in Phase 3 studies

Table 6.17: TEAEs of cardiac disorders in Phase III studies																	
		Phase III DB (13-0001)						Phase III Open label (13-0003)									
		PBO		RBP300/100 mg		RBP 300/300		De novo 300/Flex			PBO Roll-over 300/F		RBP 100 Roll-over 300/Flex		RBP 300 Roll over 300/Flex		
		N=100		N=203		N=201		N=412			N=32		N=112		N=113		
AE Severity	Preferred term	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	Any TEAEs	5	5%	9	4%	9	4%	12	3%	0	0%	1	1%	4	4%		
MILD	Bradycardia	0	0%	0	0%	1	0%	2	0%	0	0%	0	0%	0	0%	0	0%
MILD	Electrocardiogram QT prolonged	0	0%	2	1%	2	1%	2	0%	0	0%	1	1%	0	0%	0	0%
MILD	Electrocardiogram ST-T change	0	0%	0	0%	0	0%	2	0%	0	0%	0	0%	1	1%	0	0%
MILD	Heart rate increased	1	1%	0	0%	2	1%	2	0%	0	0%	0	0%	2	2%	0	0%
MILD	Sinus arrhythmia	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MILD	Sinus bradycardia	0	0%	0	0%	0	0%	2	0%	0	0%	0	0%	0	0%	0	0%
MILD	Sinus tachycardia	1	1%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MILD	Supraventricular extrasystoles	0	0%	0	0%	1	0%	1	0%	0	0%	0	0%	0	0%	0	0%
MILD	Tachycardia	1	1%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MILD	Ventricular extrasystoles	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Bradycardia	0	0%	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Bundle branch block right	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Electrocardiogram QT prolonged	0	0%	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Electrocardiogram T wave abnormal	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Supraventricular tachycardia	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Tachycardia	1	1%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
MODERATE	Wolff-Parkinson-White syndrome	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
SEVERE	Acute myocardial infarction	0	0%	1	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
SEVERE	Myocardial infarction	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	1%	0	0%

8.6. Safety Analyses by Demographic Subgroups

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

Table 51: Adverse Events Event Occurrence & Proportion Report for Sex Reporting Events with at least Overall 2% Occurrence in Phase 3 DB study (13-0001)

	Sex		
	F	M	Total
	Count (%)	Count (%)	Count (%)
Total	N=168	N=336	N=504
Gastrointestinal disorders	45(26.8%)	63(18.8%)	108(21.4%)
Constipation	14 (8.3)	21 (6.3)	35 (6.9)
Diarrhoea	3 (1.8)	12 (3.6)	15 (3)
Nausea	22 (13.1)	17 (5.1)	39 (7.7)
Toothache	6 (3.6)	8 (2.4)	14 (2.8)
Vomiting	17 (10.1)	17 (5.1)	34 (6.7)
General disorders and administration site conditions	47(28%)	59(17.6%)	106(21%)
Drug withdrawal syndrome	9 (5.4)	13 (3.9)	22 (4.4)
Fatigue	12 (7.1)	11 (3.3)	23 (4.6)
Injection site erythema	8 (4.8)	7 (2.1)	15 (3)
Injection site pain	9 (5.4)	16 (4.8)	25 (5)
Injection site pruritus	19 (11.3)	17 (5.1)	36 (7.1)
Pain	6 (3.6)	6 (1.8)	12 (2.4)

No demographic interactions on safety signals were identified.

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

8.7. **Specific Safety Studies/Clinical Trials**

No specific study or clinical trial was conducted to evaluate specific safety concerns for this NDA

8.8. **Additional Safety Explorations**

8.8.1. **Human Carcinogenicity or Tumor Development**

Safety data Included in this NDA did not reveal any potential issues related to human Carcinogenicity or tumor development.

8.8.2. **Human Reproduction and Pregnancy**

No formal clinical studies on the use in pregnancy and lactation have been conducted with RBP-6000. Twenty pregnancies were reported (19 study subjects and 1 partner of a study subject) in the RBP-6000 clinical development program as of the NDA data cut-off date. There was 1 report of neonatal drug withdrawal syndrome in a male neonate born to a subject in the 300/100 mg treatment group in the Ph3DB study. A total of 6 pregnancies were reported in Phase 3 DB study (13-0001) and 12 pregnancies was reported in Phase 3 OL study (13-0003). One pregnancy was reported as exposed via her male partner who was in RBP-6000 300/100 mg group in the Phase 3 DB study. All female subjects with pregnancy were discontinued from the studies. There was one case of spontaneous abortion reported in in subject (b) (6) in Phase 3 OL study. Causality was assessed by reviewing CRF and narrative summaries provided by the Applicant. This subject (b) (6) had urine pregnancy test positive 22 days after the first injection of RBP-6000 at dose of 300 mg and spontaneous abortion occurred 29 days after RBP-6000 injection. There was temporal relationship between the event and RBP-6000 exposure. However, the causal relationship between the spontaneous abortion event and maternal exposure of RBP-6000 can not be established as there were many confounders for this event. The subject was current smoker smoking tobacco, cannabinoid and methamphetamine, all of which may increase risks of spontaneous abortion.

8.8.3. **Pediatrics and Assessment of Effects on Growth**

Indivior has received an orphan drug designation for buprenorphine used for the indication of opioid dependence. The application is exempt from PREA requirements.

8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Buprenorphine is controlled Schedule III of the Controlled Substances Act. Evaluation of the specific risks of this new formulation, including extraction studies, was undertaken by the Applicant. A complete abuse liability assessment report is provided in this NDA and was reviewed by the Controlled Substance Staff (CSS) reviewers.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

No post-marketing data are available for RBP-6000 because it is not yet approved for use.

8.9.2. Expectations on Safety in the Postmarket Setting

The product has been administered by a health care provider in a clinical setting during the clinical development period. There are no data on take-home use or self-administration of the product by patients. There is a risk that patients, many of whom have a history of intravenous drug abuse, could improperly self-administer the product via the IV route if they were to have access to the product, which might cause life-threatening consequences.

While some of the risks of RBP-6000 are similar to those of the approved transmucosal buprenorphine products, RBP-6000 has a higher potential for adverse consequences of IV misuse or abuse than existing transmucosal buprenorphine products for the following reasons.

- RBP-6000 may be less subject to abuse via snorting (the most common route of abuse of transmucosal buprenorphine products) due to the difficulty of converting it to powder.
- RBP-6000 contains a large dose of buprenorphine (100 mg or 300 mg) without naloxone in a prefilled syringe and could be appealing to IV drug users.
 - o More than 40% of patients in clinical trials reported injection drug use in the past.
 - o In-vivo and in-vitro analyses showed that buprenorphine was easily extracted from RBP-6000 (b) (4).
 - o RBP-6000 could also be injected IV as-is, from the pre-filled syringe.

No human and animal data for IV use of RBP-6000 were included in the NDA submission. However, the Applicant has demonstrated that injection of RBP-6000 into tubing containing dog blood leads to immediate clogging. It is likely that if RBP-6000 were injected IV, an occlusion would form due to rapid solidification of the formulation when placed in aqueous fluid. An occlusion can cause local tissue damage or necrosis, which could cause secondary embolism and may present a risk of pulmonary embolism if it migrates to the lung.

Based on the factors described, the product should be administered by a health care provider in a clinical setting and an appropriate REMS would be needed to prevent the product from being in the hands of the patient prior to administration.

Other safety issues that might arise in the post-marketing setting are related to the prolonged action of the depot. It is predicted that detectable buprenorphine levels may be present for months after a single depot injection, and potentially six months or longer after steady-state is attained. This has implications for patients experiencing adverse drug reactions, drug-drug interactions, or a need for opioid analgesia. There is minimal information both about the

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

duration of action and how the action could be terminated (i.e., through removal)

8.9.3. **Additional Safety Issues From Other Disciplines**

No additional safety issues beyond those associated with the REMS and the safety issues described throughout this review of safety are under evaluation.

8.10. **Integrated Assessment of Safety**

Major safety data were collected from 848 subjects who received RBP-6000 300/300 mg or RBP-300/100 mg or RBP-6000 300/Flex SC injection in the Phase 3 double-blind study and the Phase 3 open-label, long term safety study. The safety database for RBP-6000 met ICH criteria for the treatment of chronic disease as more than 500 patients were exposed to RBP-6000 for more than 6 months and more than 100 patients were exposed to RBP-6000 at doses of 300 mg for more than one year cumulatively. The identified risks of RBP-6000 include central nervous system (CNS) effects, gastrointestinal (GI) effects, hepatic effects and injection site reactions and all of these risks are expected. The overall safety experience of RBP-6000 is consistent with the safety profile of buprenorphine. The local injection tolerability is consistent with other approved products using the ATRIGEL Delivery System as most of injection site reactions were mild to moderate. However, it appears that the RBP-6000 300/300 mg regimen was less well tolerated compared to the RBP-6000 300/100 mg regimen as evidenced by a higher percentage of TEAEs of injection site reaction and abnormal liver enzymes post-baseline (ALT \geq 3X ULN, or AST \geq 3X ULN) reported in the RBP-6000 300/300 mg group, and more early drop outs occurring in the RBP-6000 300 /300 mg group due to TEAEs in the Phase 3 DB study. The most common TEAEs leading to drug discontinuation included elevated liver enzymes, injection site reactions, sedation, constipation, somnolence, lethargy, and drug withdrawal syndrome. In the Phase 3 OL study, a total of 49 (7.3%) subjects required dose reduction from 300 mg to 100 mg due to TEAEs. The most common TEAEs leading to drug dose reduction included abnormal liver function tests, sedation, constipation, nausea, fatigue and headache. Analysis of the drug concentration-QT relationships indicated that there is not likely to be a risk of clinically significant cardiac conduction effects.

Overall, review of safety database did not reveal any new safety signals despite the higher exposure of RBP-6000.

9. Advisory Committee Meeting and Other External Consultations

A Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting was held on October 31, 2017 to discuss

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

NDA 209819, RBP-6000 (Buprenorphine -ATRIGEL monthly depot) and its safety and efficacy for the proposed indication of maintenance treatment of opioid dependence. The following specific discussion topics and voting questions were posed to the committee for deliberation, and embodied the unresolved issues about which advisory committee consultation was sought:

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

Yes: 17 No: 2 Abstain: 0

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

Yes: 13 No: 6 Abstain: 0

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

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

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

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

Yes: 18 No: 1 Abstain: 0

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

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

There was intensive discussion about the role of the RBP-6000 300/300 mg regimen, given the similarity in efficacy results between the RBP-6000 300/300 mg and RBP-6000 300/100 mg and more frequent adverse events in the high dosing regimen RBP-6000 300/300 mg. While some patients such as injection drug users might need the higher exposure buprenorphine level for effective treatment, definitive evidence is lacking. The Committee recommended a post-marketing study to be performed to define the population that will benefit from the high dosing regimen 300/300 mg.

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

The Committee also agreed that an appropriate REMS needs to be implemented to prevent the product from being in the hands of the patient prior to administration.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

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

The following are recommendations for the labeling.

- INDICATION AND USAGE

The proposed indication for RBP-6000 is: “RBP-6000 is indicated for the treatment of moderate-to-severe opioid use disorder in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product and should be used as part of a complete treatment program that includes counseling and psychosocial support.” (b) (4)

(b) (4)

The recommended indication for RBP-6000 is below:

RBP-6000 is indicated for the treatment of moderate-to-severe opioid use disorder in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product, and had dose-stabilization for a minimum of 7 days. RBP-6000 should be used as part of a complete treatment program that includes counseling and psychosocial support

- **DOSAGE AND ADMINISTRATION**

The proposed Dosage and Administration section instructs providers that “The recommended dosing regimen for RBP-6000 is 300 mg monthly for the first 2 months followed by maintenance treatment of 100 mg or 300 mg monthly based on the clinical condition of the patient.” (b) (4)

Therefore, the labeling should convey that the preferred regimen for most patients would be 100 mg monthly (after two monthly injections of 300 mg to rapidly achieve a blocking level). The 300 mg monthly maintenance dose is recommended only for patients that for whom benefits outweigh the risk as judged by the clinicians.

- **WARNINGS AND PRECAUTIONS**

Compared with current Suboxone labeling, the proposed warnings and precautions lacks the following information:

(b) (4)

6.1 Clinical Trials Experience

The Applicant states that

(b) (4)

the following table replaces corresponding table 2 and table 3.

Table 52: Adverse Drug Reactions for Phase 3 Double-Blind Study: \geq 2% of Subjects Receiving RBP-6000

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

^{(b) (4)} system/preferred term	PLACEBO	RBP-6000 300/100 mg	RBP-6000 300/300 mg
	Count (%)	Count (%)	Count (%)
Total	N=100	N=203	N=201
Gastrointestinal disorders	12(12%)	51(25.1%)	45(22.4%)
Constipation		19 (9.4)	16 (8)
Nausea	5 (5)	18 (8.9)	16 (8)
Vomiting	4 (4)	19 (9.4)	11 (5.5)
General disorders and administration site conditions	17(17%)	40(19.7%)	49(24.4%)
Fatigue	3 (3)	8 (3.9)	12 (6)
Investigations	2(2%)	21(10.3%)	19(9.5%)
Alanine aminotransferase increased		2 (1)	10 (5)
Aspartate aminotransferase increased		7 (3.4)	9 (4.5)
Blood creatine phosphokinase increased	1 (1)	11 (5.4)	5 (2.5)
Gamma-glutamyl transferase increased	1 (1)	6 (3)	8 (4)
Nervous system disorders	7(7%)	35(17.2%)	25(12.4%)
Headache	6 (6)	19 (9.4)	17 (8.5)
Sedation		7 (3.4)	3 (1.5)
Somnolence		10 (4.9)	4 (2)

Table 53: Injection site adverse drug reactions reported ≥ 2 subjects in the Phase 3 studies (Adapted from Applicant's table)

Preferred term, n (%)	13-0001 (Ph3DB)			13-0003 (Ph3OL)				All
	RBP-6000 300/300 (N = 201)	RBP-6000 300/100 (N = 203)	Placebo (N = 100)	Roll-over			De-novo	Phase 3 Total RBP-6000 (N=848)
				RBP-6000 300 → RBP-6000 300/Flex (N=113)	RBP-6000 100 → RBP-6000 300/Flex (N=112)	Placebo → RBP-6000 300/Flex (N=32)	RBP-6000 300/Flex (N=412)	
Subjects with any ^{(b) (4)}	38 (18.9%)	28 (13.8%)	9 (9.0%)	6 (5.3%)	13 (11.6%)	2 (6.3%)	61 (14.8%)	140 (16.5%)
Injection site pain	12 (6.0%)	10 (4.9%)	3 (3.0%)	4 (3.5%)	2 (1.8%)	2 (6.3%)	33 (8.0%)	61 (7.2%)
Injection site pruritus	19 (9.5%)	13 (6.4%)	4 (4.0%)	2 (1.8%)	6 (5.4%)	1 (3.1%)	17 (4.1%)	56 (6.6%)
Injection site erythema	6 (3.0%)	9 (4.4%)	0	1 (0.9%)	4 (3.6%)	0	21 (5.1%)	40 (4.7%)
Injection site induration	2 (1.0%)	2 (1.0%)	0	0	1 (0.9%)	0	7 (1.7%)	12 (1.4%)
Injection site bruising	2 (1.0%)	2 (1.0%)	0	0	0	0	2 (0.5%)	6 (0.7%)
Injection site swelling	1 (0.5%)	2 (1.0%)	0	1 (0.9%)	1 (0.9%)	0	1 (0.2%)	6 (0.7%)
Injection site discomfort	1 (0.5%)	1 (0.5%)	0	0	0	0	3 (0.7%)	5 (0.6%)
Injection site reaction	1 (0.5%)	0	0	0	3 (2.7%)	0	1 (0.2%)	5 (0.6%)
Injection site cellulitis	0	1 (0.5%)	0	0	0	0	2 (0.5%)	3 (0.4%)
Injection site infection	1 (0.5%)	0	1 (1.0%)	0	0	0	2 (0.5%)	3 (0.4%)

14.1 Clinical Studies

The clinical studies section was revised ^{(b) (4)} and to be consistent with current labeling guidelines.

At the time of this review, the final labeling is still being developed.

10.2. Nonprescription Drug Labeling

Not applicable for this NDA review.

11. Risk Evaluation and Mitigation Strategies (REMS)

In the NDA submission, the Applicant proposed a REMS with a Medication Guide, ETASU, implementation system and a timetable for submission of assessments.

Dr. Somya Dunn compared the Applicant's REMS proposal and the Agency's REMS proposal. The following is the summary from her review:

“Applicant's REMS proposal

The Applicant's rationale for their proposed REMS includes that the product contains high doses of medication (100 mg or 300 mg of buprenorphine) and the long acting formulation increases the risk for CNS depression if used concomitantly with other CNS depressants. The high doses and lack of naloxone may appeal to those who abuse opioids by injecting them. The Applicant also studied the extractability of RBP-6000. If the product was diverted and extraction was attempted, they found that the buprenorphine could be easily extracted with common household solvents. To limit the ability for RBP-6000 to be diverted, misused and abused, they proposed a REMS with a Medication Guide and ETASU. The proposed ETASU would use the existing federal requirements to limit the dispensing of the medication to certain healthcare settings that are DEA registrants or specially-qualified prescribers in office practice settings who are Drug Addiction Treatment Act of 2000 (DATA 2000)-waived. Their distribution of the product would exclude dispensing in retail pharmacy settings, which they believe would prevent dispensing directly to the patient for self-administration. Their proposed REMS goal is to:

- Mitigate the risks of accidental overdose, misuse and abuse
- Inform prescribers, pharmacists and patients of the serious risks of RBP-6000
- Inform prescribers, pharmacists and patients about the long acting nature of RBP-6000

The Applicant asserts that once injected as directed into the subcutaneous space, the product is not readily misused, abused and diverted. They propose to minimize misuse, abuse and diversion of RBP-6000 by requiring that it is dispensed only in certain healthcare settings and administered by an HCP. The Applicant is proposing that RBP-6000 only be

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

dispensed or sold to prescribers who are DATA 2000-waived in an office-based setting and hospitals, integrated health system out-patient clinics, long-term care facilities, Department of Defense facilities, prisons, and inpatient psychiatric units that are DEA registrants. In addition, RBP-6000 could be administered in federally approved opioid treatment programs (OTPs) where a DATA 2000-waiver is not required. They propose to use already existing databases such as the DEA Registration Validation website or the Substance Abuse and Mental Health Services Administration (SAMHSA) Buprenorphine Practitioner Verification websites to verify the status of the facility and/or prescriber of their ability to prescribe, receive and store the product. The Applicant is also proposing to include ETASU that includes safe use and monitoring similar to that seen in the other programs for outpatient buprenorphine for MAT.

The Applicant has proposed the following materials relevant to their proposed REMS:

- *HCP Brochure*—this material summarizes important safety issues and messages needed to manage and counsel patients about safe use of this product for prescribers and pharmacists.
- *Appropriate Use Checklist*—a tool for prescribers to use with patients at the office visits.
- *Patient Alert Card*—a card for patients to carry that alerts HCPs that they have are on RBP-6000 therapy and some of the characteristics of this treatment that HCPs should be aware of.
- Letters to prescribers, pharmacists and professional societies informing them about the REMS

Agency's REMS proposal

The RBP-6000 risk profile differs from the other buprenorphine products indicated for MAT that are approved with REMS. The Agency is particularly concerned about the potential risks associated with this product, because it is an injectable form of buprenorphine and will be available in prefilled syringes with needles in the same package. It is ready to inject and also easier to inject than other formulations, and is in a final product configuration that is typically dispensed for outpatient use. As noted by the Applicant, there is inherently a potential high risk for abuse and misuse with this product since, given the proposed indication, many patients prescribed this medication will have a history of IV drug abuse. More than 40% of subjects in the clinical studies reported history of injection drug use.

Clinical Review

Fang Emily Deng, MD., MPH., MS

NDA 209819

Sublocade (Buprenorphine) extended -release injection

Importantly, as it is not the proposed route of administration, IV injection of RBP-6000 was not studied in the clinical program. The Agency is concerned about the potential downstream adverse events (AEs) that may result from IV injection of RBP-6000 (i.e. embolus, rapid dissolution resulting in high levels of opioid).

Because the RBP-6000 risk profile differs from the approved buprenorphine products indicated for MAT, the Agency is considering a REMS that focuses on the risks that are specific to RBP-6000.

The goal of the Agency's proposed REMS is to mitigate potential adverse consequences due to intravenous self-administration by the patient by ensuring that RBP-6000 is only dispensed and administered in certain healthcare settings by a HCP. Accidental exposure is not included in the Agency's proposed goals because the injectable formulation and administration in healthcare settings reduces this risk.

The Agency proposes a REMS that limits dispensing of RBP-6000 to certain settings that have a DATA-waived prescriber or are DEA registrants to prevent dispensing directly to the patient for home use. This approach is consistent with the Applicant's proposal. Additionally, the Agency is considering requiring healthcare settings that include both inpatient and outpatient services and integrated health care systems (e.g., Kaiser Permanente, Department of Defense) to become certified to dispense RBP-6000 if they wish to use this treatment. A one-time certification would include a requirement that those settings put policies and procedures in place to prevent RBP-6000 from being dispensed directly to the patient for self-administration at home. The addition of the one-time healthcare setting certification does add some burden to these particular settings, but would ensure that they are aware and agree to institute policies and procedures to prevent dispensing of RBP-6000 directly to patients."

At the time of this review, the specific REMS materials are being developed, to include an enrollment form for health care facilities, a fact sheet to inform stakeholders about the REMS program and how to obtain the product, and similar informational materials.

12. Postmarketing Requirements and Commitments

Postmarketing requirements are still under discussion by the review team. The Applicant may be asked to develop information on which patients would benefit from higher doses, and to explore whether dosing less frequently than monthly might be feasible. The Applicant may also be asked to explore whether RBP-6000 could be initiated at the first clinical visit (without initial dose stabilization).

13. Appendices

13.1. References

None

13.2. Financial Disclosure

The Applicant's submission included the completed "Certification: Financial Interests and Arrangements of Clinical Investigators" form (Form FDA 3455). The Applicant indicated that the investigators at each site are certified as having no Financial Arrangement as defined in 21 CFR 54.2.

The table below are lists of clinical investigators across all clinical studies.

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Table 54: Clinical investigators list in the financial disclosure certification form

Scott Daniel Segal, MD	RB-US-10-0011
Bradley D. Vince, DO	RB-US-11-0020
Bradley D. Vince, DO	RB-US-12-0005
Otto R. Dueno, MD	RB-US-13-0001
Valentin Isacesu, MD	RB-US-13-0001
Saleem Ishaque, MD	RB-US-13-0001
Vishaal Mehra, MD, CPI	RB-US-13-0001
Haydn Mikel Thomas, MD	RB-US-13-0001
Gita Pujari, MD, ADM, CMRO	RB-US-13-0001
Shishuka Malhotra, MD	RB-US-13-0001
Scott Daniel Segal, MD, MBA	RB-US-13-0001
David R. Hassman, DO	RB-US-13-0001
Eduardo Cifuentes, MD	RB-US-13-0001
Kent Steven Hoffman, DO	RB-US-13-0001
Rishi Kakar, MD	RB-US-13-0001
Ricky Stuart Mofsen, DO Formerly Sandra Daniela Duarte- Sckell, MD	RB-US-13-0001
Genie L. Bailey, MD	RB-US-13-0001
Boyde J. Harrison, MD	RB-US-13-0001
Richard D. Knapp, DO	RB-US-13-0001
Aaron V. Blackledge, MD	RB-US-13-0001
Kyle Kampman, MD	RB-US-13-0001
Rajinder Shiwach, MD	RB-US-13-0001
Amit K. Vijapura, MD	RB-US-13-0001
David P. Walling, PhD	RB-US-13-0001
Katharina L. Wiest, PhD, MSPH	RB-US-13-0001
Marvin Lane Peyton, MD	RB-US-13-0001
Daniel Rutrick, MD	RB-US-13-0001
Gregory Seal, MD	RB-US-13-0001
Rakesh Ranjan, MD	RB-US-13-0001
Joseph A. Kwentus, MD	RB-US-13-0001
Michael J. Biunno, MD	RB-US-13-0001
Jesse M. Carr, MD	RB-US-13-0001
Scott Robert Bartley, MD	RB-US-13-0001
Peter Paul Ventre, MD	RB-US-13-0001
Lawrence S. Levinson, MD	RB-US-13-0001
Jelena Kunovac, MD, MS	RB-US-13-0001
Brent Boyett, DO, DMD	RB-US-13-0001
James L. Andersen, MD	RB-US-13-0001
George Konis, MD	RB-US-13-0001
Debra J. Kelsh, MD	RB-US-13-0002
Otto R. Dueno, MD	RB-US-13-0003
Valentin Isacescu, MD	RB-US-13-0003
Saleem Ishaque, MD	RB-US-13-0003
Vishaal Mehra, MD, CPI	RB-US-13-0003

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

Haydn Mikel Thomas, MD	RB-US-13-0003
Gita Pujari, MD, ADM, CMRO	RB-US-13-0003
Shishuka Malhotra, MD	RB-US-13-0003
Scott Daniel Segal, MD, MBA	RB-US-13-0003
David R. Hassman, DO	RB-US-13-0003
Eduardo Cifuentes, MD	RB-US-13-0003
Kent Steven Hoffman, DO	RB-US-13-0003
Rishi Kakar, MD	RB-US-13-0003
Daniel M. Gruener, MD Formerly Ricky Stuart Mofsen, DO	RB-US-13-0003
Genie L. Bailey, MD	RB-US-13-0003
Boyde J. Harrison, MD	RB-US-13-0003
Richard D. Knapp, DO	RB-US-13-0003
Kyle M. Kampman, MD	RB-US-13-0003
Rajinder Shiwach, MD	RB-US-13-0003
Amit K. Vijapura, MD	RB-US-13-0003
David P. Walling, PhD	RB-US-13-0003
Katharina L. Schuman Wiest, PhD, MSPH	RB-US-13-0003
Marvin Lane Peyton, MD	RB-US-13-0003
Daniel Rutrick, MD	RB-US-13-0003
Gregory Seal, MD	RB-US-13-0003
Rakesh Ranjan, MD	RB-US-13-0003
Joseph A. Kwentus, MD	RB-US-13-0003
Michael J. Biunno, MD	RB-US-13-0003
Jesse M. Carr, MD	RB-US-13-0003
Scott Robert Bartley, MD	RB-US-13-0003
Peter Paul Ventre, MD	RB-US-13-0003
Lawrence S. Levinson, MD	RB-US-13-0003
Jelena Kunovac	RB-US-13-0003
Brent Boyett	RB-US-13-0003
Angelo Sambunaris, MD	RB-US-13-0003
James L. Andersen, MD	RB-US-13-0003
George Konis, MD	RB-US-13-0003
Corinna Gamez, MD	RB-US-13-0003
Leon I Rosenberg, MD	RB-US-13-0003
Elias H. Sarkis, MD	RB-US-13-0003
Daniel F. Chueh, MD	RB-US-13-0003
Jason L. Andersen, DO	RB-US-13-0003
Michael R. Liebowitz, MD	RB-US-13-0003
Debra J. Kelsh, MD	RB-US-13-0006

Covered Clinical Study (Name and/or Number): RB-US-10-0011, RB-US-11-0020, RB-US-12-0005, RB-US-13-0001, RB-US-13-0003

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>85</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		

Clinical Review
 Fang Emily Deng, MD., MPH., MS
 NDA 209819
 Sublocade (Buprenorphine) extended -release injection

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____

Significant payments of other sorts: _____

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in S

Sponsor of covered study: _____

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Clinical Review
Fang Emily Deng, MD., MPH., MS
NDA 209819
Sublocade (Buprenorphine) extended -release injection

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

/s/

FANG E DENG
11/10/2017

CELIA J WINCHELL
11/10/2017