FDA ADVISORY COMMITTEE MEETING BRIEFING DOCUMENT

RBP-6000

(extended-release buprenorphine)

JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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TABLE OF CONTENTS

Table of Contents 2
List of Tables 5
List of Figures 7
List of Abbreviations 9
1 Executive Summary 11
1.1 Introduction 11
1.2 Background on Opioid Use Disorder and Medication-Assisted Treatment 11
1.3 Rationale for Product Development 14
1.4 Pharmacokinetics and Dose Selection 14
1.5 Efficacy Findings 16
1.6 Safety Findings 20
1.7 Risk Evaluation and Management Strategy (REMS) 22
1.8 Conclusions 22
2 Background on Opioid Use Disorder 24
2.1 Opioid Use Disorder 24
2.2 Current Treatment Landscape 25
2.3 Unmet Patient Need 27
3 RBP-6000 Product Description and Clinical Development 29
3.1 Proposed Indication 29
3.2 Treatment Administration and Dosing Regimen 29
3.3 Mechanism of Action 31
3.4 Objectives of Clinical Development Program 31
3.5 Clinical Studies 31
4 Clinical Pharmacology 34
4.1 Background 34
4.2 Overview of Clinical Pharmacology Program 35
4.3 Pharmacokinetic Characteristics 36
4.3.1 Phase 1/2 SAD and MAD Studies 36
4.3.2 Effect of Intrinsic Factors 36
4.3.3 Population PK Modeling 37
4.4 Studies Supporting Dose Selection for Phase 3 Studies 38
4.4.1 SAD and MAD Studies 38

4.4.2 Opioid Blockade Study (Study 13-0002) 39
4.4.3 Rationale for Phase 3 Dosing Regimens 41
4.5 Pharmacokinetics of Phase 3 Dosing Regimens 41
5 Phase 3 Clinical Efficacy 43
5.1 Pivotal Phase 3 Double-Blind Study (Study 13-0001) 43
5.1.1 Study Design 43
5.1.1.1 Efficacy Endpoints 45
5.1.1.2 Statistical Analyses 47
5.1.2 Subject Disposition 48
5.1.3 Subject Demographic and Baseline Characteristics 49
5.1.4 Primary Endpoint – Percentage Abstinence 50
5.1.4.1 Additional Analyses of Percentage Abstinence (UDS + Self-report) 51
5.1.4.2 Abstinence at Week 24 and Total Weeks Abstinent 53
5.1.4.3 Subgroup Analyses of Percentage Abstinence 53
5.1.5 Key Secondary Endpoint 55
5.1.6 Other Secondary Endpoints 56
5.1.6.1 Opioid Craving VAS 56
5.1.6.2 COWS 58
5.1.6.3 SOWS 58
5.1.6.4 Percentage Abstinence Based on UDS Only 59
5.1.6.5 Percentage Abstinence Based on Self-Reports Only 60
5.1.7 Employment Status 60
5.1.8 Exposure-Response Analyses 61
5.2 Phase 3 Open-Label Study 13-0003 63
5.2.1 Study Design 63
5.2.2 Maintenance of Efficacy 64
5.3 Efficacy Conclusions 65
6 Clinical Safety 66
6.1 Treatment Exposure 66
6.2 Treatment-Emergent Adverse Events 67
6.2.1 Serious Adverse Events 69
6.2.2 Deaths 70

6.2.3 TEAEs Leading to Study Discontinuation 70
6.2.4 TEAEs Leading to Dose Reduction 72
6.3 Injection Site Reactions 73
6.3.1 Injection Site TEAEs 73
6.3.2 Injection Site Tolerability Assessments 75
6.3.2.1 Local Injection Site Assessments 75
6.3.2.2 Subject-Reported Injection Site Pain (VAS) 77
6.4 Depot Removal 77
6.5 Electrocardiograms 77
6.6 Liver Chemistry 79
6.7 Respiratory Depression and RBP-6000 Overdose 82
6.8 Overdose with Other Drugs 82
6.9 Safety by Subgroup 82
6.10 Safety Conclusions 82
7 Risk Evaluation and Mitigation Strategy (REMS) for RBP-6000 83
7.1 Background 83
7.2 Considerations in the Design of the RBP-6000 REMS Program 84
7.3 Product Distribution 84
7.4 Objectives of the RBP-6000 REMS Program 85
7.5 Proposed Elements of the RBP-6000 REMS Program 87
7.6 Adverse Event Monitoring, Analysis, and Reporting 89
7.7 Intervention Strategies 90
7.8 Implementation System and Timetable for REMS Assessment 90
8 Benefit-Risk Analysis 91
9 References 93
10 Appendices 97
10.1 Inclusion and Exclusion Criteria for the Ph3DB Study 97
10.2 Subject Disposition in the Phase 3 Studies 100
10.3 TEAEs Reported in Prescribing Information for SUBOXONE 101
10.4 Narrative for Death in the Phase 3 Double-Blind Study 102
10.5 eDISH Plots for Ph3DB and Ph3OL Studies 103

LIST OF TABLES

Table 1: Summary Statistics for Percentage Abstinence in the Ph3DB Study 18
Table 2: Clinical Studies in the RBP-6000 Development Program 32
Table 3: Estimated Mean Buprenorphine 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....42
Table 4: Summary of Efficacy Endpoints in the Ph3DB Study 47
Table 5: Subject Disposition – All Randomized Subjects 48
Table 6: Demographic and Baseline Characteristics in the Ph3DB Study (FAS) 49
Table 7: Drug Use History in the Ph3DB Study (FAS) 50
Table 8: Summary Statistics for Percentage Abstinence from Week 5 through Week 24 (UDS + Self-report) in the Ph3DB Study (FAS)....51
Table 9: Percentage Abstinence from Week 5 through Week 24 by Subgroup (FAS)....54
Table 10: Secondary Endpoint Analysis by Mixed Model for Repeated Measures for Change from Baseline to Week 24 in the Ph3DB Study (FAS)....56
Table 11: Percentage of Urine Samples Negative for Opioids from Week 5 through Week 24 in the Ph3DB Study (FAS)....59
Table 12: Percentage of Self-Reports Negative for Illicit Opioid Use from Week 5 Through Week 24 in the Ph3DB Study (FAS) 60
Table 13: Employment Status at Baseline and End of Study in the Ph3DB Study....61
Table 14: Estimated Mean Buprenorphine 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....61
Table 15: Demographic and Baseline Characteristics in the Ph3OL Study....64
Table 16: Overall Summary of TEAEs in the Ph3DB Study 67
Table 17: TEAEs Reported in at Least 5% of Subjects in Any Treatment Group During the Ph3DB Study....68
Table 18: Overall Summary of TEAEs in the Treatment Phase of the Ph3OL Study 68
Table 19: TEAEs Reported in ≥ 5% of Subjects in Any Subject Group in the Treatment Phase of the Ph3OL Study 69
Table 20: Serious TEAEs in the Ph3DB Study....69
Table 21: Serious TEAEs in the Ph3OL Study 70
Table 22: TEAEs that Led to Study Treatment Discontinuation in the Ph3DB Study 71
Table 23: TEAEs that Led to Study Treatment Discontinuation in the Treatment Phase of the Ph3OL Study....71
Table 24: TEAEs Leading to RBP-6000 Dose Reduction in the Ph3OL Study 73

Table 25: Injection Site TEAEs at Any Assessed Time Point in the Phase 3 Studies 74
Table 26: Injection Site Assessment Scale 75
Table 27: Injection Site Tolerability (Grades Moderate or Severe) at Any Assessed Time Point in the Phase 3 Studies 76
Table 28: Summary of Local Injection Site Visual Analog Scale (VAS) Pain Scores after the First Injection in the Ph3DB Study 77
Table 29: Liver Chemistry Results in the Phase 3 Studies 80
Table 30: Liver Chemistry Results in Ph3DB Study of RBP-6000 and in Hepatic Safety Study of SUBOXONE 81
Table 31: Benefit-Risk Analysis of RBP-6000 91
Table 32: Phase 3 Individual and Pooled Studies: Subject Disposition 100
Table 33: Adverse Events (≥5%) by Body System and Treatment Group in a 16-Week Study.101
Table 34: Adverse Events (≥ 5%) by System Organ Class and Treatment Group in a 4-Week Study 102

LIST OF FIGURES

Figure 1: Mean Drug-Liking VAS Scores in the Opioid Blockade Study 15
Figure 2: Primary Efficacy Endpoint Results in Ph3DB Study....18
Figure 3: Number of Subjects Negative and Positive for Illicit Opioid Use by Visit without Imputation for Missing Data (FAS) 19
Figure 4: RBP-6000 Prefilled Syringe....30
Figure 5: Relationship between Whole Brain μORO and Buprenorphine Plasma Concentration (Nasser 2014) 35
Figure 6: Opioid Blockade Study Design....39
Figure 7: Mean Buprenorphine Plasma Concentrations from Opioid Blockade Study....40
Figure 8: Mean Drug-Liking VAS Scores from Opioid Blockade Study (Study 13-0002) 40
Figure 9: Mean Buprenorphine Plasma Concentrations from Ph3DB Study 41
Figure 10: Mean Buprenorphine Plasma Concentrations among Subjects Receiving 12 Consecutive Monthly 300-mg Doses 42
Figure 11: Design of the Ph3DB Study 45
Figure 12: Kaplan-Meier Analysis of Retention in the Ph3DB Study (FAS) 49
Figure 13: Primary Efficacy Endpoint: Percentage Abstinence from Week 5 through Week 24 (UDS + Self-report) in the Ph3DB Study (FAS) 51
Figure 14: Number of Subjects Negative and Positive for Illicit Opioid Use (UDS + Self-report) by Visit without Imputation for Missing Data (FAS) 52
Figure 15: Percentage Abstinence from Week 5 through Week 24 (UDS + Self-report) in the Ph3DB Study without Imputation for Missing Data (FAS)....52
Figure 16: Percentage of Subjects Abstinent (by UDS + Self-report) by Week in the Ph3DB Study (FAS) 53
Figure 17: Key Secondary Efficacy Endpoint: Percentage of Subjects Meeting Criterion for Treatment Success (≥ 80% Negative UDS + Self-report) in the Ph3DB Study (FAS) 55
Figure 18: Estimated Mean Opioid Craving VAS Scores from Week 1 through Week 24 in the Ph3DB Study Based on MMRM (FAS) 57
Figure 19: Number of Subjects with Opioid Craving VAS Scores of 0, 1-5, 6-20, or >20 mm by Visit (FAS) 57
Figure 20: Estimated Mean Clinical Opiate Withdrawal Scale (COWS) Scores from Week 1 through Week 24 in the Ph3DB Study Based on MMRM (FAS)....58
Figure 21: Estimated Mean Subjective Opiate Withdrawal Scale (SOWS) Scores from Baseline through Week 24 in the Ph3DB Study Based on MMRM (FAS)....59
Figure 22: Exposure-Response Analysis for Abstinence 62
Figure 23: Exposure-Response Analysis for Opioid Craving VAS 62
Figure 24: Exposure-Response Analysis for COWS....63

Figure 25: Percentage of Subjects Abstinent by Subject Groups and Study Weeks for Roll-Over Subjects in the Ph3OL Study 65
Figure 26: Predicted Mean (90% CI) Delta QTc at Concentration Levels Corresponding to Repeated Monthly Doses of 100-mg, 300-mg, and 2× 300-mg (600 mg) RBP-6000 ..79
Figure 27: eDISH Plots of Peak Total Bilirubin (×ULN) and Peak ALT (×ULN) in Ph3DB Study 103
Figure 28: eDISH Plots of Peak Total Bilirubin (×ULN) and Peak AST (×ULN) in Ph3DB Study 103
Figure 29: eDISH Plots of Peak Total Bilirubin (×ULN) and Peak ALT (×ULN) in Ph3OL Study 104
Figure 30: eDISH Plots of Peak Total Bilirubin (×ULN) and Peak AST (×ULN) in Ph3OL Study 104

LIST OF ABBREVIATIONS

Abbreviation	Definition
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{tau}	area under the plasma concentration-time curve over the dosing interval
BMI	body mass index
CARA	Comprehensive Addiction and Recovery Act
C_{avg}	average plasma concentration over the defined interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration over the defined interval
CI	confidence interval
CMQ	Customized MedDRA Query
COWS	Clinical Opiate Withdrawal Scale
CNS	central nervous system
CSA	Controlled Substances Act
DATA-2000	Drug Addiction Treatment Act of 2000
DILI	drug-induced liver injury
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
eDISH	evaluation of drug-induced serious hepatotoxicity
ECG	electrocardiogram
ER	extended-release
ETASU	elements to assure safe use
FAS	Full Analysis Set
FDA	Food and Drug Administration
FTIH	first time in human
HCl	hydrochloride
HCP	healthcare professional
HIV	human immunodeficiency virus
IDC	individual drug counseling
IM	intramuscular
IQR	interquartile range
ITT	intention-to-treat
IV	intravenous
LOCF	last observation carried forward
LS	least squares
MAD	multiple ascending dose

MAT	medication-assisted treatment
MCID	minimal clinically important difference
MMRM	mixed model for repeated measures
MW	molecular weight
µORO	µ-opioid receptor occupancy
NDA	New Drug Application
NESARC	National Epidemiologic Survey of Alcohol and Related Conditions
NIDA	National Institute on Drug Abuse
NMP	N-methyl-2-pyrrolidone
NSDUH	National Survey on Drug Use and Health
OB	opioid blockade
OUD	opioid use disorder
OTP	opioid treatment program
PD	pharmacodynamic(s)
PET	positron emission tomography
Ph3DB	Phase 3 double-blind
Ph3OL	Phase 3 open-label
PI	prescribing information
PK	pharmacokinetic(s)
PLGH	poly(DL-lactide-co-glycolide)
PT	preferred term
REMS	Risk Evaluation and Mitigation Strategy
SAD	single ascending dose
SAMHSA	Substance Abuse and Mental Health Services Administration
SAP	statistical analysis plan
SAE	serious adverse event
SC	subcutaneous(ly)
SD	standard deviation
SL	sublingual(ly)
SOWS	Subjective Opiate Withdrawal Scale
TEAE	treatment-emergent adverse event
TLFB	Timeline Followback
T_{max}	time to maximum plasma concentration
UDS	urine drug screen
ULN	upper limit of normal
US	United States
VAS	visual analog scale

1 EXECUTIVE SUMMARY

1.1 Introduction

RBP-6000 is an extended-release (ER) formulation of buprenorphine, a μ-opioid partial agonist, for the treatment of opioid use disorder (OUD). As proposed, RBP-6000 is indicated for the treatment of moderate-to-severe OUD in patients who have undergone induction with a transmucosal (sublingual [SL] or buccal) buprenorphine-containing product to suppress opioid withdrawal signs and symptoms. RBP-6000 should be used as part of a complete treatment plan that includes counseling and psychosocial support. RBP-6000 was studied in and is intended for patients attempting to recover from OUD, who may or may not have tried medication-assisted treatment (MAT) in the past.

RBP-6000 utilizes buprenorphine and the ATRIGEL® Delivery System, which consists of a biodegradable polymer, poly(DL-lactide-co-glycolide) with a carboxylic acid end group (PLGH), dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). The ATRIGEL Delivery System has been used in 7 other drug products approved by the United States (US) Food and Drug Administration (FDA).

RBP-6000 is administered once monthly by subcutaneous (SC) injection in the abdominal region and provides sustained plasma levels of buprenorphine over the dosing interval. RBP-6000 is injected as a solution, and subsequent precipitation of the polymer creates a solid depot containing the buprenorphine. After initial formation of the depot, buprenorphine is released via diffusion from, and the biodegradation of, the depot.

RBP-6000 is available in dosage strengths of 100-mg and 300-mg buprenorphine and is provided in a prefilled syringe to a healthcare professional (HCP) to be administered to a patient in a healthcare setting. 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.

1.2 Background on Opioid Use Disorder and Medication-Assisted Treatment

Opioid Use Disorder

Opioid use disorder is a neurobehavioral syndrome characterized by repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and physical consequences (Substance Abuse and Mental Healt Services Administration 2004). Opioid use disorder is a chronic, relapsing disease that has grown to epidemic proportions. In 2016, there were an estimated 2.1 million individuals with OUD (prescription pain reliever or heroin use disorder) in the US (Center for Behavioral Health Statistics and Quality 2016). The number of opioid overdose deaths (including prescription opioids, heroin, and synthetic opioids like fentanyl) have quadrupled since 1999 (Centers for Disease Control 2016). Opioid use disorder also has extremely high costs to individuals, families, and society, with an estimated $78.5 billion expended in 2013 (Florence et al. 2016).

OUD can also be an enormous burden on the quality of life for those afflicted as well as their friends and families. Patients with OUD consistently report poor mental and physical health-related quality of life (Cranmer et al. 2016; Bray et al. 2017). Opioid use disorder is also associated with significant burden to society through unemployment, homelessness, family disruption, loss of economic productivity and social instability (World Health Organization et al. 2004; Callahan et al. 2015).

Background on Medication-Assisted Treatment

MAT, which has decades of evidence to support its efficacy and safety, is recommended by national treatment guidelines as the current standard of care for OUD (Kampman et al. 2015). MAT combines counseling/behavioral therapy with medications to provide a whole-patient approach to the treatment of OUD. OUD is a chronic, relapsing condition where the clinical course typically includes periods of exacerbation and remission, but the patient is never disease-free. MAT is similar to treatments for other chronic conditions like diabetes and hypertension in that long-term disease management is challenging and adherence to treatment is often incomplete.

The 3 FDA-approved medications available for MAT of OUD are naltrexone, methadone, and buprenorphine. Naltrexone is a competitive antagonist that functions by binding to and blocking activity at μ-opioid receptors. As an antagonist, naltrexone does not control symptoms of withdrawal or reduce craving, so it is only indicated for the prevention of relapse to opioid dependence for patients who have already achieved complete abstinence from opioids. Methadone is a μ-opioid full agonist and buprenorphine is a μ-opioid partial agonist. Both methadone and buprenorphine bind to and activate μ-opioid receptors to relieve craving, suppress opioid withdrawal signs and symptoms, and block the subjective effects of other opioids if used on top of treatment. Buprenorphine elicits effects on the central nervous system (CNS), such as euphoria and respiratory depression, to a lesser extent than full agonists like methadone. With buprenorphine, these pharmacologic effects increase linearly with increasing doses until reaching a plateau. This “ceiling effect” lowers the risk of misuse, dependency, and other side effects of buprenorphine compared to μ-opioid full agonists such as methadone (Substance Abuse and Mental Health Services Administration 2016).

MAT with oral methadone or transmucosal buprenorphine requires daily dosing. Adherence to a daily medication regimen can be difficult for many patients. One study found that adherence to buprenorphine MAT was 32% in the year following treatment initiation (Tkacz et al. 2014), while another study found that abstinence with daily buprenorphine ranged from 36% to 43% depending on the definition of abstinence used (Ruetsch et al. 2017). Not surprisingly, lower adherence to daily dosing of an OUD treatment is associated with higher rates of relapse to illicit opioid use. The likelihood of relapse to illicit opioid use was approximately 10 times greater when adherence to daily buprenorphine dosing fell below 80% (Tkacz et al. 2012). Additionally, daily dosing may not result in a consistent drug plasma level, especially if doses are missed.

Relationship between Buprenorphine Plasma Concentration and Opioid Blockade

Research has shown that substantial occupancy of brain μ-opioid receptors is necessary to achieve opioid blockade, that is, the inhibition of the positive subjective effects (e.g., drug liking) of exogenous opioids. Opioid blockade can be provided by drugs that occupy μ-opioid receptors, such as methadone and buprenorphine. Brain imaging studies have shown that the extent of μ-opioid receptor occupancy (μORO) required to achieve opioid blockade is higher than that needed to suppress the signs and symptoms of withdrawal. The suppression of signs and symptoms of withdrawal appears to require ≥ 50% μORO, which is associated with buprenorphine plasma concentrations ≥ 1 ng/mL. Opioid blockade appears to require ≥ 70-80% μORO, which is associated with buprenorphine plasma concentrations ≥ 2-3 ng/mL (Greenwald et al. 2014; Nasser et al. 2014).

The degree of μORO, and thus the buprenorphine plasma concentration, required to achieve opioid blockade may also be influenced by factors such as genetics, concomitant medical conditions (e.g., chronic pain, hepatic disease), psychiatric conditions, or comorbid abuse of non-opioid substances (e.g., nicotine, cocaine), or abuse of high doses of opioids (Greenwald et al. 2014).

Depending on dosage, transmucosal buprenorphine can achieve the target levels of 2-3 ng/mL, but those concentrations may not be sustained over the entire 24-hour dosing interval. In one brain imaging study, daily dosing of 16 mg SL buprenorphine resulted in a mean μORO of 70% at 4 hours after administration, which dropped to 46% at 28 hours post-dose (Greenwald et al. 2007).

Public Health Concerns of Buprenorphine Diversion, Misuse, Abuse, and Accidental Pediatric Exposure

Buprenorphine, like other opioids, is subject to diversion, misuse, and abuse. Most buprenorphine used illicitly in the US is diverted from prescriptions written for the treatment of OUD. Buprenorphine was also one of the most common opioids identified among drug cases submitted to and identified by federal, state, and local forensic laboratories, after heroin, oxycodone, fentanyl, and hydrocodone (US Department of Justice Drug Enforcement Administration 2016). A large survey at US treatment centers found that buprenorphine was the fourth most commonly diverted opioid medication (Cicero et al. 2014). In-depth follow-up interviews found 2 primary motivations for buprenorphine use outside of a treatment program: to prevent withdrawal sickness (e.g., “to hold me over during work/social events”), or to use buprenorphine as a substitute to get high when the individual’s drug of choice was not available (Cicero et al. 2014). In addition, buprenorphine medications dispensed for take-home use have also been implicated in accidental poisoning of children. From 2008-2015, the CDC estimates that there were more than 8,100 emergency department visits for buprenorphine/naloxone ingestion by children under 6 years of age, most of which (62%) required hospitalization (Centers for Disease Control 2016).

1.3 Rationale for Product Development

The goal of the RBP-6000 development program was to identify safe and efficacious dosing regimens of a depot product that delivered sustained buprenorphine plasma concentrations to provide opioid blockade throughout a monthly dosing interval without the need for supplemental transmucosal buprenorphine. Such a product would benefit providers and patients by not only reducing the burden of daily medication adherence to help patients achieve abstinence from illicit opioids, but also encourage compliance with the goals of MAT by removing the ability to periodically discontinue medication (i.e., taking a "drug holiday") to overcome the opioid blocking effects and therefore experience the positive subjective effects of an illicit opioid. These advantages were expected to provide patients with an important treatment option for this challenging condition.

In addition to providing a therapeutic alternative to currently-available buprenorphine treatments, RBP-6000 also provides a new method of drug delivery and administration that can be expected to provide public health benefits. RBP-6000 would be provided to HCPs through a restricted distribution system and administered only by HCPs in a healthcare setting. This closed system is intended to help protect patients, treatment providers, and society from the risks of buprenorphine diversion, misuse, abuse, and accidental pediatric exposure.

1.4 Pharmacokinetics and Dose Selection

The development program utilized the scientific knowledge on the relationship between buprenorphine plasma levels, whole brain μORO, and the clinical effects of withdrawal suppression and opioid blockade in order to maximize the benefits of buprenorphine for patients with OUD. The clinical pharmacology and pharmacokinetics (PK) of RBP-6000 were evaluated in 7 clinical studies in subjects with OUD to assess single-dose and multiple-dose PK and exposure-response relationships for achieving efficacy.

Plasma PK and μORO data from a multiple ascending dose (MAD) study were used to evaluate the PK and pharmacodynamic (PD) profiles of repeated SC injections at doses of 50, 100, 200, and 300 mg every 28 days in 89 opioid-dependent, treatment-seeking subjects. The key findings with the various doses were:

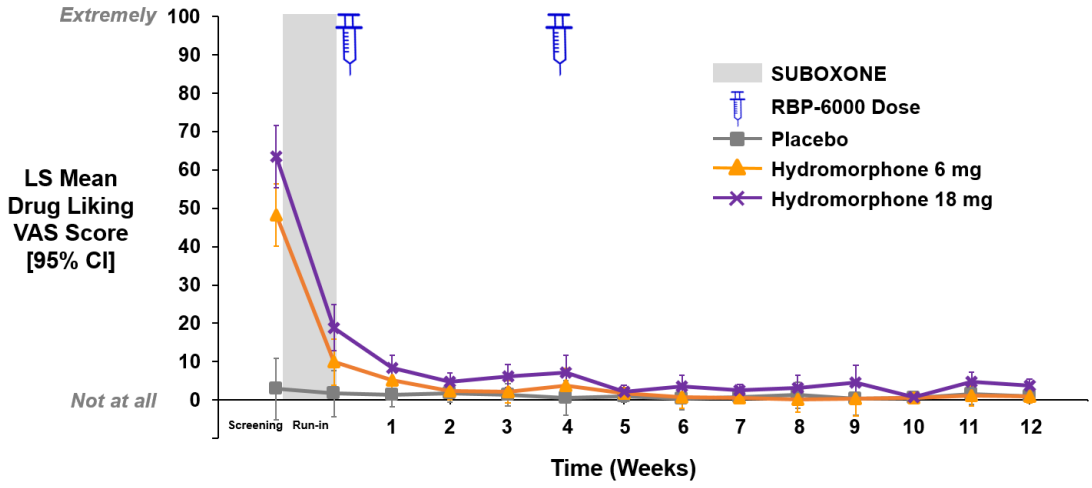
- **RBP-6000 300 mg** provided an average buprenorphine plasma concentration of ~2 ng/mL after the first dose. Subsequent monthly doses provided sustained average plasma concentrations above 2-3 ng/mL and μORO above 70%, the buprenorphine levels and μORO associated with opioid blockade in prior studies (Greenwald et al. 2014; Nasser et al. 2014).
- **RBP-6000 100 mg** could provide average buprenorphine concentrations of 2-3 ng/mL at steady-state after 6 monthly doses. It was determined that 2 initial consecutive monthly doses of 300 mg were needed to achieve target buprenorphine levels more quickly, which could be maintained thereafter with monthly administration of 100-mg doses.

Dose selection for the Phase 3 studies was also informed by an opioid blockade study, which was designed in consultation with the FDA to test the hypothesis that monthly administration of RBP-6000 300 mg would block the subjective effects of a μ-opioid full agonist. In this study, 39 non-treatment-seeking subjects with OUD were initially inducted on SUBOXONE SL film, and were required to have been maintained at stable daily dosages between 8 and 24 mg of SL buprenorphine. RBP-6000 300 mg was administered on Day 1 and Day 29. Subjects were challenged with placebo, 6-mg hydromorphone, or 18-mg hydromorphone given IM, at various times during the study. Hydromorphone is a short-acting μ-opioid full agonist commonly used in human laboratory studies as a prototypic opioid agonist. Each challenge with hydromorphone/placebo was administered in a randomized sequence on 3 consecutive days such that all subjects experienced each of the 2 hydromorphone doses or placebo in a blinded fashion.

The first hydromorphone/placebo challenge was administered during screening to confirm that subjects were able to discriminate between hydromorphone and placebo, and to determine subject eligibility for participation in the study. The second challenge was administered before the first dose of RBP-6000 during the last 3 days of SUBOXONE sublingual film administration. Subsequent challenges were administered at the end of each week after RBP-6000 administration for up to 8 weeks after the second and last dose of RBP-6000.

Subjects completed a battery of subjective-effects visual analog scales (VAS) (e.g., “drug liking”, “good drug effect”, “high”) at multiple times during each hydromorphone/placebo challenge session. The primary outcome measure was the Drug Liking VAS (“Do you like the drug?”) measured on a 0-100 mm scale where 0 indicated “not at all” and 100 indicated “extremely”. Figure 1 illustrates the results for Drug Liking during the study.

Figure 1: Mean Drug-Liking VAS Scores in the Opioid Blockade Study



At screening, prior to induction with SUBOXONE, the mean Drug Liking VAS scores for hydromorphone challenges were high (49-65 mm). At the end of SUBOXONE induction and run-in, prior to RBP-6000 administration, mean Drug Liking scores for the two hydromorphone challenges were lower than baseline, but were still higher than placebo, suggesting that SUBOXONE had not provided full opioid blockade. At all subsequent visits following treatment

with RBP-6000 300 mg, Drug Liking VAS scores for hydromorphone 6 mg and 18 mg were similar to placebo (all mean values < 10 mm on 0-100 mm scale), demonstrating that RBP-6000 achieves opioid blockade, successfully blocking the subjective effects of a μ-opioid full agonist when used on top of RBP-6000 over the monthly dosing interval from the first dose of treatment.

The totality of results from the ascending dose studies and opioid blockade study provided support for the dose selection in the Phase 3 program:

- RBP-6000 300 mg, which provides opioid blockade from the first dose of treatment, was selected as the 2 initial monthly doses for the Phase 3 dosing regimens
    - Monthly maintenance doses of RBP-6000 100 mg could sustain target buprenorphine concentrations associated with opioid blockade (≥ 2-3 ng/mL) following the 2 initial doses of 300 mg
    - Monthly maintenance doses of RBP-6000 300 mg could provide buprenorphine plasma concentrations above target levels of 2-3 ng/mL, consistent with the literature which suggests that patients with certain clinical conditions may require higher buprenorphine exposure

1.5 Efficacy Findings

The Phase 3 double-blind, placebo-controlled study (Ph3DB; Study 13-0001) is the pivotal efficacy study for RBP-6000.

Ph3DB Study Design

The Ph3DB study was a double-blind, randomized, placebo-controlled, multicenter study designed to assess the efficacy, safety, and tolerability of multiple monthly SC injections of RBP-6000 (first 2 monthly injections of 300 mg followed by 4 monthly injections of either 300 mg or 100 mg) in subjects with a diagnosis of moderate-to-severe OUD who were seeking MAT. The study inclusion criteria allowed for enrollment of subjects aged 18-65 years who were generally healthy with a body mass index (BMI) of 18-35 kg/m^2 who had not been on MAT for the last 90 days. Subjects were excluded if they had current diagnoses requiring long-term treatment with opioids, a recent history of suicidality, or current/history of clinically significant medical problems.

Following an initial screening period of up to 2 weeks, subjects entered a run-in period and were inducted on SUBOXONE sublingual film. The purpose of the SUBOXONE run-in was to ensure that subjects could tolerate buprenorphine (e.g., no hypersensitivity) prior to receiving a monthly injection and to avoid precipitating opioid withdrawal. Induction with a transmucosal buprenorphine-containing product prior to receiving RBP-6000 is consistent with the proposed indication for use.

A total of 504 subjects who were successfully inducted on SUBOXONE sublingual film and met the inclusion criteria were randomized 4:4:1:1 to 1 of 4 treatment regimens administered via SC injection every 28 (± 2) days (note: placebo was the ATRIGEL Delivery System without buprenorphine):

- 300-mg RBP-6000 (Doses 1-6) + Individual Drug Counseling (IDC), hereafter referred to as the 300/300-mg dosing regimen
- 300-mg RBP-6000 (Doses 1-2) and 100-mg RBP-6000 (Doses 3-6) + IDC, hereafter referred to as the 300/100-mg dosing regimen
- 300-mg volume-matched placebo (Doses 1-6) + IDC
- 300-mg volume-match placebo (Doses 1-2) and 100-mg volume-matched placebo (Doses 3-6) + IDC

Supplemental dosing with any buprenorphine-containing product was not permitted during the study after randomization. Abstinence from opioid use was assessed weekly using a urine drug screen (UDS) combined with self-reported opioid use from the Timeline Followback (TLFB) interview (i.e., UDS + self-report). Either measure showing use (UDS or TLFB) was considered a week that was positive for opioid use.

All treatment regimens included manual-guided individual behavioral counseling/IDC at least once per week, continuing through the end of study visit. An IDC reference manual was provided to each site, and therapy was administered by an appropriately qualified and trained staff member who remained blinded to the subjects' UDS results.

Primary statistical analyses treated missing data from weekly UDS and weekly self-reported opioid use from the TLFB interview as positive for illicit opioid use. If a subject prematurely discontinued the study, all subsequent visits were treated as positive for opioids. The primary and key secondary efficacy endpoints were analyzed under the intention-to-treat (ITT) principle and included all randomized subjects. For efficacy and safety analyses, the 2 placebo regimens were pooled into a single placebo group in accordance with the pre-specified statistical analysis plan (SAP). In agreement with FDA, 15 subjects from a single site were excluded from efficacy analyses due to site compliance issues that resulted in site closure by the sponsor. These 15 subjects are included in safety analyses.

Primary Efficacy Endpoint

The primary efficacy endpoint of the Ph3DB study was percentage abstinence from illicit opioid use (UDS + self-report) from Week 5 to Week 24. For each subject, percentage abstinence was calculated as the percentage of weekly visits (from Week 5 to Week 24) in which paired UDS and self-reports from the TLFB interview were both negative for opioids. The inclusion of a "grace period" over the first 4 weeks of treatment was instituted in recognition of the known challenges associated with treating this patient population, allowing subjects the opportunity to more fully engage in treatment. Significance testing between groups was conducted using the Wilcoxon rank-sum test.

The pivotal study met its primary efficacy endpoint. Both RBP-6000 groups showed significantly greater percentage abstinence compared to the placebo group ($P < 0.0001$ for both RBP-6000 groups compared to placebo). Figure 2 shows the distribution of percentage abstinence by group. The vast majority (84%) of placebo subjects never achieved abstinence

from opioids at any point during the treatment period (i.e., 0% abstinence), while a substantial proportion of subjects in the RBP-6000 groups were abstinent for a considerable amount of the treatment period.

Figure 2: Primary Efficacy Endpoint Results in Ph3DB Study

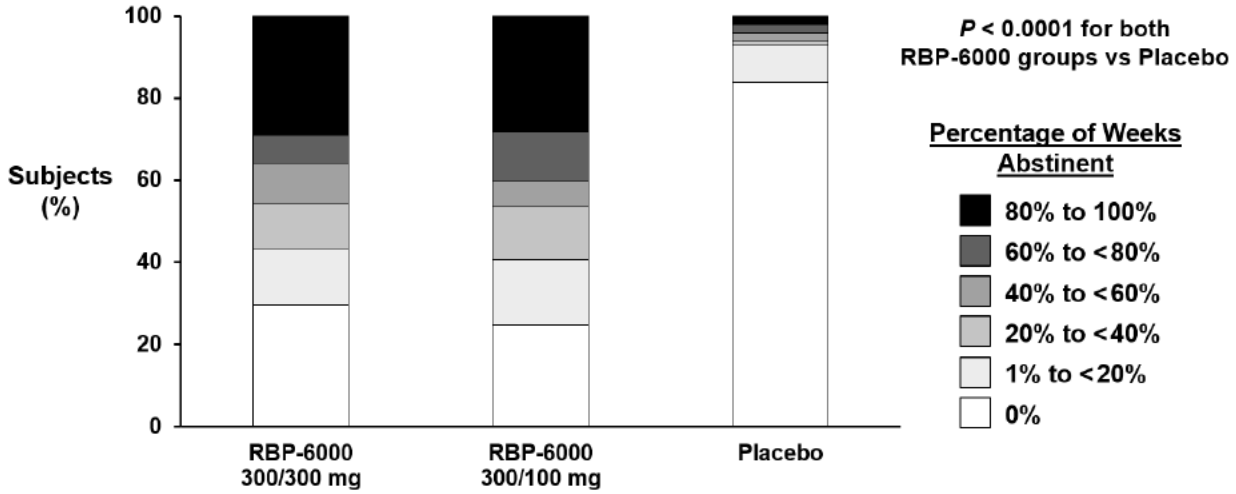


Table 1 provides summary statistics of the percentage abstinence by the 3 study groups. The mean and median percentage abstinence were higher in the RBP-6000 groups than in the placebo group. Subjects were approximately 10 times as likely to have ≥ 50% abstinence, ≥ 80% abstinence, and 100% abstinence on either RBP-6000 regimen compared to the placebo group.

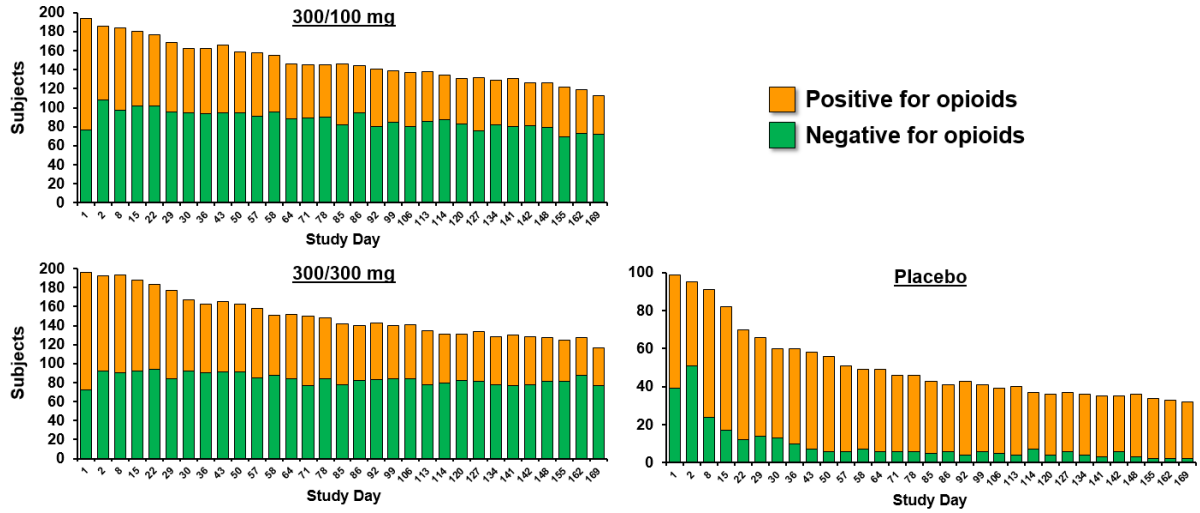
Table 1: Summary Statistics for Percentage Abstinence in the Ph3DB Study

Group	Mean (SD)	Median (IQR)	Percent of Subjects with Abstinence			
			0%	≥ 50%	≥ 80%	100%
Placebo	5% (17%)	0% (0% - 0%)	84%	4%	2%	1%
300/100 mg	43% (38%)	33% (5% - 80%)	25%	44%	28%	13%
300/300 mg	41% (40%)	30% (0% - 85%)	30%	42%	29%	12%

SD = standard deviation. IQR = interquartile range (25th and 75th percentiles).

Figure 3 provides another representation of abstinence data from the study, illustrating the observed number of subjects who were positive and negative for illicit opioid use (UDS + self-report) at each study visit without imputation for missing data (note: the height of the bars decreases as subjects discontinued the study). This figure demonstrates that abstinence was achieved by a considerable number of subjects immediately after starting treatment with RBP-6000 and a substantial number of subjects were abstinent at each visit throughout the study. In the placebo group, few subjects were abstinent after the first few days of the treatment period.

Figure 3: Number of Subjects Negative and Positive for Illicit Opioid Use by Visit without Imputation for Missing Data (FAS)



Note: Study Day 1 is the end of the SUBOXONE run-in period. Study Day 2 reflects 24 hours after the first SC injection of RBP-6000 or placebo.

Key Secondary Efficacy Endpoint

The key secondary endpoint was treatment success, defined as any subject with ≥ 80% abstinence from illicit opioid use (UDS + self-report) between Week 5 and Week 24. The RBP-6000 groups had statistically significantly higher proportions of subjects who achieved at least 80% abstinence compared with the placebo group (300/300 mg: 29% and 300/100 mg: 28% vs. placebo: 2%; $P < 0.0001$), and thus the key secondary efficacy endpoint was met.

Other Efficacy Endpoints

Results from additional secondary endpoints, including the Opioid Craving Visual Analog Scale (VAS), Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), provided further support for the efficacy of RBP-6000. Based on repeated-measures analysis, the percentage of subjects who had control of withdrawal symptoms throughout the treatment period (COWS ≤ 12 on a 0-48 scale) was > 99% in both RBP-6000 groups. The percentage of subjects who had control of opioid craving throughout the treatment period (Opioid Craving VAS ≤ 5 mm on a 0-100 mm scale) was 81% in both RBP-6000 groups.

The percentages of subjects who completed the 24-week double blind treatment period were higher for the RBP-6000 groups (300/300 mg: 64%, 300/100 mg: 62%) than the placebo group (34%). The benefits of RBP-6000 were also evident in employment status. Among subjects who completed the study, the percentage of those employed at the end of the study increased from baseline in the RBP-6000 groups (300/300 mg: +15% and 300/100 mg: +10%) and decreased in the placebo group (-5%).

Subgroup Analyses

The findings among clinical subgroups of interest were consistent with the scientific literature that some individuals require higher buprenorphine exposure and higher levels of μORO to maximize abstinence and retention in treatment. Subgroup analyses among injecting drug users suggested that the 300/300-mg regimen achieved higher percentage abstinence than the 300/100-mg regimen. Subsequent exploratory analyses determined that the percentage of injecting drug users in the study who remained abstinent for the last 4 weeks of the double-blind period, when differences in buprenorphine plasma concentrations between the two regimens were the greatest, was higher with the 300/300-mg regimen (34% [27/80]) than the 300/100-mg regimen (18% [15/84])).

Phase 3 Open-Label Safety Study

In addition to the Ph3DB study, a long-term Phase 3 Open-Label Safety Study (Ph3OL; Study 13-0003) provides additional supportive efficacy data. Interim data from the Ph3OL study suggests that targeted buprenorphine plasma concentrations and abstinence rates persist through 12 doses of RBP-6000.

Summary of Efficacy

Overall, results support the efficacy of RBP-6000 for the treatment of OUD. The opioid blockade study demonstrated that RBP-6000 300 mg blocks the positive subjective effects (e.g., drug liking) of hydromorphone, a μ-opioid full agonist, if used on top of RBP-6000, from the first dose and throughout the monthly dosing interval. The Ph3DB study demonstrated that both the 300/300-mg and the 300/100-mg RBP-6000 dosing regimens helped a substantial proportion of subjects achieve abstinence from illicit opioids, control symptoms of withdrawal, and reduce opioid craving without the need for supplemental buprenorphine. The efficacy findings support the use of 2 initial consecutive monthly 300-mg doses followed by monthly maintenance of either 100-mg or 300-mg doses. Subgroup findings from the Ph3DB study were consistent with the prior scientific literature that some individuals (e.g., injecting drug users) may benefit from higher buprenorphine exposure and higher levels of μORO to maximize abstinence and retention in treatment.

1.6 Safety Findings

The safety profile of RBP-6000 is consistent with the well-established safety profiles of other buprenorphine-containing products, with the exception of injection site reactions, which were anticipated with a product administered via SC injection.

The safety database for RBP-6000 includes 1,083 subjects with OUD who received at least 1 injection of RBP-6000 across all studies. Of these, 848 subjects received RBP-6000 in the Ph3DB and Ph3OL studies. As of the database cutoff date for the Ph3OL study, 557 subjects received at least 6 injections of RBP-6000 and 138 subjects received 12 injections in the Phase 3 studies. There were 532 subjects with at least 24 weeks of exposure, and 87 subjects with at least 48 weeks of exposure.

Overall, the treatment-emergent adverse event (TEAE) profile was consistent with the known safety profile for buprenorphine, with the exception of anticipated injection site reactions. The most common TEAEs (reported in ≥ 5% of RBP-6000 subjects in the Ph3DB study) were headache, constipation, nausea, injection site pruritus, vomiting, insomnia, upper respiratory tract infection, injection site pain, nasopharyngitis, and fatigue. Treatment-emergent adverse events leading to discontinuation were reported in ≤ 5% of subjects in all treatment groups. In the Ph3DB study, the incidence of injection site reactions was 18.9% in the 300/300-mg group, 13.8% in the 300/100-mg group, and 9.0% in the placebo group. The higher frequency of injection site reaction TEAEs in the 300/300-mg group compared to the 300/100-mg group was likely due to the higher delivered volume (1.5 mL vs 0.5 mL) and the higher amount of buprenorphine in the 300-mg dose. Injection site reactions were nearly all mild or moderate in severity and transient, led to discontinuation in fewer than 1% of subjects, and none were reported as serious.

Elevated hepatic enzymes are consistent with the known safety profile of buprenorphine (Saxon et al. 2013; Fareed et al. 2014) and were not unexpected with RBP-6000. In the Ph3DB study, the incidence of alanine aminotransferase (ALT) more than 3 times the upper limit of normal (> 3 × ULN) was 12.4%, 5.4%, and 4.0% in the RBP-6000 300/300-mg, RBP-6000 300/100-mg, and placebo groups, respectively. The incidence of aspartate aminotransferase (AST) > 3 × ULN was 11.4%, 7.9%, and 1.0%, respectively. The incidence of total bilirubin > 2 × ULN was 0.5%, 0.5%, and 0%, respectively. There were no instances of Hy's Law (bilirubin > 2 × ULN and ALT and AST > 3 × ULN). The rates of liver enzyme elevations observed in the Ph3DB study for RBP-6000 were similar to what was reported in a large hepatic safety study of SUBOXONE conducted in 2006 by the National Institute on Drug Abuse (NIDA) (see Section 6.6 for details).

One RBP-6000 subject in a Phase 1 trial had a serious adverse event (SAE) with elevated liver enzymes and had the depot surgically removed; it was subsequently determined that this subject had new onset hepatitis C. There were no other SAEs potentially pertaining to liver dysfunction, no drug-induced liver disease, and no potential Hy's Laws cases in any subject in any of the clinical studies. Exposure-response analyses were conducted to evaluate the relationship between buprenorphine plasma concentration and the probability of ALT and AST elevations (> 3 × ULN, > 5 × ULN, and > 8 × ULN) with RBP-6000 in the Phase 3 studies. Overall, exposure-response curves were flat within the observed concentration range, which did not suggest a relationship between buprenorphine exposure and these liver chemistry elevations.

Given the known effects of buprenorphine on liver chemistry and the fact that patients with OUD are at high risk for pre-existing liver disease (e.g., Hepatitis B, C, and D; human immunodeficiency virus [HIV]; alcohol-induced liver disease), Indivior is proposing that the label for RBP-6000 include similar recommendations addressing hepatic safety as the current label for SUBOXONE. These recommendations include conducting a baseline assessment of liver chemistry, periodic monitoring of liver chemistry, and searching for an etiology should liver chemistry values rise.

In the Ph3OL study, the incidence of TEAEs in the de-novo group was similar to the active groups in the Ph3DB study. Importantly, the incidence of TEAEs in the RBP-6000 roll-over subjects from the Ph3DB study to the Ph3OL study did not increase compared to the double-blind phase, nor did new patterns of TEAEs emerge as subjects continued treatment with RBP-6000.

Overall, this analysis demonstrates that both RBP-6000 dosing regimens – 300/300 mg and 300/100 mg – have a favorable safety profile for their intended use.

1.7 Risk Evaluation and Management Strategy (REMS)

Indivior is also proposing a Risk Evaluation and Management Strategy (REMS) to promote safe and appropriate use of RBP-6000. The key elements of the RBP-6000 REMS program are consistent with the ongoing REMS for SUBOXONE, with the addition of a restricted distribution system to limit diversion. The primary goals of the REMS will be:

- to mitigate the risks of diversion, misuse, abuse, and accidental pediatric exposure;
- to inform prescribers, pharmacists, and patients about the risks associated with RBP-6000; and
- to inform prescribers, pharmacists, and patients about the long-acting nature of the RBP-6000 formulation.

Key components of the REMS include the distribution of physician and patient education materials; surveillance monitoring for diversion, misuse, and abuse; AE monitoring; intervention strategies to identify noncompliance and to work with local communities and develop specific plans of action in cases where there are concerning levels of misuse or abuse; and regular assessments of the REMS effectiveness in achieving its goals.

Several educational tools will be employed as part of the RBP-6000 REMS program, including a *Medication Guide*, *REMS Prescriber Letter*, *REMS Pharmacist Letter*, *REMS Professional Society Letter*, *Appropriate Use Checklist*, *REMS HCP Brochure*, *Patient Alert Card*, and the REMS website. More information regarding the REMS is provided in Section 7.

1.8 Conclusions

The results from the clinical program support the approval of RBP-6000 as a safe and efficacious treatment for patients attempting to recover from OUD as part of a complete treatment plan that includes counseling and psychosocial support.

The opioid blockade study demonstrated that RBP-6000 300 mg provides blockade of subjective opioid effects from the first dose over a monthly dosing interval without the need for supplemental transmucosal buprenorphine. This finding supports the proposed dosing recommendation to start all patients on 2 initial consecutive monthly doses of 300 mg to achieve buprenorphine plasma concentrations that provide opioid blockade starting from the first dose of treatment.

The Ph3DB study demonstrated that, following 2 initial monthly doses of 300 mg, both 100-mg and 300-mg maintenance doses provide sustained abstinence, control of withdrawal signs and symptoms, and reduction in opioid craving over the monthly dosing interval without the use of supplemental buprenorphine. Prior studies have found that certain patients (e.g., individuals who abuse high doses of opioids, patients with chronic pain or psychiatric conditions) require higher buprenorphine doses to achieve opioid blockade and maximize abstinence and treatment retention. Consistent with those prior findings, injecting drug users in the Ph3DB study had higher percentage abstinence with the higher maintenance dose. Therefore, the proposed labeling for RBP-6000 reflects that some patients may benefit from the 300-mg maintenance dose. The decision about the appropriate maintenance dose for an individual patient should be based on a benefit-risk assessment in the context of the factors that are known to influence the efficacy of buprenorphine.

Importantly, RBP-6000 was well-tolerated, and the clinical program identified no new or unexpected safety findings. The safety profile of RBP-6000 was consistent with currently marketed FDA-approved transmucosal buprenorphine products with the exception of the anticipated injection site reactions.

Several findings from the clinical program, as well as unique attributes of the product, suggest that RBP-6000 represents an important advance in the treatment of patients with OUD:

- RBP-6000 provides opioid blockade from administration of the first dose throughout the 1-month dosing interval
- The monthly dosing regimen reduces the burden on patients to adhere to a daily dosing regimen
- As a monthly depot injection, patients would not be able to skip daily doses and defeat the opioid blocking effects in order to experience the effects of an illicit opioid (i.e., taking a “drug holiday”)
- RBP-6000 can help patients achieve abstinence, control withdrawal signs and symptoms, and reduce craving for opioids without the need for supplemental buprenorphine
- As a product administered by an HCP in a healthcare setting and distributed through a restricted distribution system RBP-6000 can be expected to reduce the diversion, misuse, abuse, and accidental pediatric exposure associated with self-administered transmucosal buprenorphine products

The totality of the data from the clinical program demonstrates that RBP-6000 provides sustained buprenorphine plasma concentrations that lead to effective opioid blockade, clinically meaningful benefits, and a favorable safety profile for individuals with OUD.

2 BACKGROUND ON OPIOID USE DISORDER

Summary

- Opioid use disorder (OUD) is a chronic, relapsing disease characterized by compulsive seeking or use of opioids despite adverse social, psychological, and physical consequences.
- The prevalence of OUD has increased over the past decade, with an estimated 2.0 million people in the US with a prescription pain reliever use disorder and 0.6 million with heroin use disorder.
- Medication-assisted treatment (MAT) with methadone or buprenorphine is an effective treatment option for OUD; however, methadone and transmucosal buprenorphine require adherence to daily dosing, which can be a challenge for many patients.
- Self-administered, take-home medications for OUD, such as transmucosal buprenorphine, are subject to abuse, misuse, diversion, and accidental pediatric exposure.
- A new treatment option for OUD that maintains opioid blockade over a monthly dosing interval and that is only distributed to and administered by approved healthcare professionals (HCPs) can be expected to improve treatment response and reduce the risks of abuse, misuse, diversion, and accidental pediatric exposure.

2.1 Opioid Use Disorder

Opioid use disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is a neurobehavioral syndrome characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and physical consequences. Patients with OUD consistently report poor mental and physical health-related quality of life (Cranmer et al. 2016; Bray et al. 2017). Furthermore, OUD results in significant burden to the individual and society through unemployment, homelessness, family disruption, loss of economic productivity, social instability, and criminal activities (World Health Organization et al. 2004; Callahan et al. 2015).

Abuse of opioids and resulting OUD have increased significantly over the past decade. In 2016, there were an estimated 2.1 million individuals in the United States (US) with OUD (prescription pain reliever or heroin use disorder) based on the most recent data from the National Survey on Drug Use and Health (NSDUH) (Center for Behavioral Health Statistics and Quality 2016). Data from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) show that the adult prevalence of nonmedical prescription OUD doubled from 0.4% in 2002 to 0.8% in 2013 (Saha et al. 2016). Adding to the impact of OUD, deaths from opioid overdoses have resulted in a public health crisis. Provisional CDC data suggests that there were over 53,000 opioid overdose deaths in the US in 2016, which is more than quadruple the number of opioid deaths in 1999 (Centers for Disease Control 2017). While deaths related to prescription opioids have remained relatively stable since 2010, there has been an increase in deaths related to heroin and synthetic opioids (Centers for Disease Control 2016).

OUD is associated with considerable costs to individuals, families and society. The total US societal costs of prescription opioid abuse were estimated at $78.5 billion in 2013 (Florence et al. 2016). Workplace costs accounted for $20.4 billion (26%), healthcare costs accounted for $29.0 billion (37%), criminal justice costs accounted for $7.9 billion (10%), and costs for fatal overdoses accounted for $21.2 billion (27%). Mean annual direct healthcare costs for opioid abusers are an estimated $15,500 per year higher than non-abusers (Florence et al. 2016).

2.2 Current Treatment Landscape

Despite the growing epidemic of OUD and its impact on health and productivity, most of those with OUD do not receive treatment. A recent publication estimated that only 29% of those with a prescription OUD ever receive treatment (Saha et al. 2016). Among those with OUD who receive treatment, the median delay from onset of OUD to first attempt to seek treatment was 3.8 years in the US (Blanco et al. 2013).

Medication-assisted treatment for OUD is intended to help patients achieve abstinence from illicit opioid use by either controlling withdrawal signs and symptoms, reducing craving, blocking the subjective effects of opioids if used on top of treatment, or all 3. MAT combines counseling/behavioral therapy with medications to provide a whole-patient approach to the treatment of OUD. There are currently 3 FDA-approved medications for the treatment of OUD: naltrexone, methadone, and buprenorphine.

- **Naltrexone** is a competitive antagonist that functions by binding to and blocking activity at μ-opioid receptors. As an antagonist, naltrexone does not control symptoms of withdrawal or reduce craving, so it is indicated for the prevention of relapse to opioid dependence for patients who have already undergone opioid detoxification (Substance Abuse and Mental Health Services Administration 2016). Naltrexone is contraindicated for patients who are currently undergoing opioid withdrawal or patients who are engaged in current opioid use. Naltrexone can be administered as a tablet taken daily or as a monthly intramuscular (IM) injection.
- **Methadone** is a μ-opioid full agonist that binds to and activates μ-opioid receptors to relieve craving, suppress opioid withdrawal signs and symptoms, and block the subjective effects of other opioids. Methadone can be administered daily as a liquid or tablet at an opioid treatment program (OTP) such as a methadone clinic or dispensed for take-home use (Substance Abuse and Mental Health Services Administration 2016). Patients starting on methadone treatment must generally travel to a certified clinic every day to receive their daily dose, which can present a barrier to treatment for some patients who have difficulty securing reliable transportation or who live in rural areas. Methadone is contraindicated for patients who are hypersensitive to methadone, patients with respiratory depression, and those with acute bronchial asthma or hypercarbia.
- **Buprenorphine** is a μ-opioid partial agonist that also activates μ-opioid receptors and relieves craving, suppresses withdrawal signs and symptoms, and blocks the subjective effects of other opioids. Because it is a partial agonist, it produces effects such as euphoria and respiratory depression to a lesser extent than full agonists like methadone; these

pharmacologic effects increase linearly with increasing doses until they reach a plateau, beyond which no further increase in activity is elicited. This "ceiling effect" lowers the risk of misuse, dependency, and other side effects (e.g., respiratory depression and sedation) for buprenorphine compared to full agonists like methadone (Substance Abuse and Mental Health Services Administration 2016). Buprenorphine is most frequently dispensed for patients to self-administer as a daily transmucosal (sublingual [SL] or buccal) medication, and is sometimes provided through OTPs. Unlike methadone treatment, buprenorphine may be prescribed or dispensed in physicians' offices. Under the Drug Addiction Treatment Act of 2000 (DATA-2000), qualified physicians in the US can provide buprenorphine treatment for OUD in various settings, including an office, community hospital, and other venues. Buprenorphine recently became available in the form of a 6-month subdermal implant, PROBUPHINE®, which is indicated for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of no more than 8 mg per day of SUBUTEX or SUBOXONE sublingual tablet or generic equivalent). PROBUPHINE is not appropriate for new entrants to treatment. Buprenorphine is contraindicated in patients who are hypersensitive to buprenorphine (or naloxone for buprenorphine-naloxone combination products).

MAT with a μ-opioid full agonist or partial agonist (e.g., methadone or buprenorphine, respectively) is an effective treatment option for OUD (Mattick et al. 2009; Mattick et al. 2014; Nielsen et al. 2016). Of the 307,180 heroin treatment admissions for OUD to publicly-funded treatment facilities in the US in 2013, 26.8% and 18.0%, respectively, involved either methadone or buprenorphine as part of the treatment plan (Substance Abuse and Mental Health Services Administration -Treatment Episode Data Set 2015).

As use of buprenorphine has become more widespread and availability increases with increasing numbers of prescriptions, diversion has become more prevalent (Lofwall et al. 2014). Rates of abuse for buprenorphine are generally lower than for μ-opioid full agonists when these products are available, and buprenorphine is infrequently described as a primary drug of abuse. Nonetheless, prevalence of buprenorphine abuse has increased markedly.

A structured survey of 10,568 individuals at over 150 treatment centers in 48 states found that buprenorphine had the fourth highest prevalence of abuse in the past month of medications studied (33% of respondents), behind oxycodone (97%), hydrocodone (80%), and alprazolam (57%) (Cicero et al. 2014). In-depth, follow-up interviews with a subset of respondents (n=106) found 2 primary motivations for buprenorphine use outside of a treatment program. The first motivation was to prevent withdrawal sickness (e.g., "to hold me over during work/social events"). The second motivation was to use buprenorphine as a substitute to get high when the individual's drug of choice was not available (Cicero et al. 2014).

Several studies point to barriers to treatment access, such as cost, location, and admission criteria for treatment programs, as key risk factors for using diverted buprenorphine (Lofwall et al. 2012; Genberg et al. 2013; Richert et al. 2015; Wright et al. 2016). Because of high rates of diversion,

physicians are often reluctant to treat certain patients with buprenorphine, or to use high enough doses, which may leave patients vulnerable to relapse.

Although most individuals who abuse buprenorphine report that they use through the intended transmucosal route of administration, approximately one-quarter to one-third of those who abuse buprenorphine in the US report injecting it (Cicero et al. 2014; Larance et al. 2014). In the US, Indivior markets buprenorphine hydrochloride (HCl) in combination with naloxone HCl dihydrate as SUBOXONE sublingual film for the treatment of opioid dependence. When taken orally or sublingually, naloxone is minimally bioavailable; however, parenteral (e.g., intravenous [IV]) administration can induce rapid opioid withdrawal signs and symptoms to deter abuse in individuals who are physically dependent on opioids.

In addition to the known risks for diversion, misuse, and abuse of self-administered buprenorphine products, there also exists the potential for accidental pediatric exposure. The uptake of buprenorphine as a treatment for OUD has been associated with a sharp rise in the number of accidental exposures among children. Between 2008-2015, there were an estimated 8,136 emergency department visits for ingestion of a buprenorphine/naloxone combination product by children aged < 6 years, three-quarters of which involved children aged 1 or 2 years (Budnitz et al. 2016). Accidental unsupervised buprenorphine ingestion among young children can have serious health consequences including CNS depression, respiratory depression, or death (Lavonas et al. 2013).

2.3 Unmet Patient Need

As mentioned above, buprenorphine abuse via injection is a significant challenge in the treatment of OUD. Because of the serious risks of human immunodeficiency virus (HIV) and hepatitis C virus infection and other complications linked to injection, it is important to develop buprenorphine formulations that cannot be readily diverted or abused by IV injection.

Medication-assisted treatment with oral methadone or transmucosal buprenorphine requires adherence to a daily dosing regimen, which can be difficult for many patients. One study found that adherence to buprenorphine MAT was 32% in the year following treatment initiation (Tkacz et al. 2014), while another study found that abstinence with daily buprenorphine ranged from 36% to 43% depending on the definition of abstinence used (Ruetsch et al. 2017). Not surprisingly, lower adherence to daily dosing is associated with higher rates of relapse to illicit opioid use. One study found that the likelihood of relapse to illicit opioid use was 10 times greater when adherence to daily dosing fell below 80% (Tkacz et al. 2012). Additionally, daily dosing may not result in consistent drug plasma levels and occupancy of μ-opioid receptors (Greenwald et al. 2007), especially if doses are missed. A parenterally-administered, extended-release buprenorphine product could improve treatment adherence compared to existing products that are administered SL or buccally on a daily basis. Furthermore, the nature of a depot product would enhance compliance by preventing a patient from being able to take a drug holiday (i.e., skipping doses to let opioid blockade diminish so they could feel the subjective effects of an illicitly-administered opioid).

Finally, access to a subcutaneous (SC) formulation of buprenorphine administered in a controlled environment may expand treatment access to patients given the reluctance of some providers to prescribe buprenorphine due to the risks of diversion, misuse, abuse, and accidental pediatric exposure of self-administered medications.

3 RBP-6000 PRODUCT DESCRIPTION AND CLINICAL DEVELOPMENT

Summary

- RBP-6000 is proposed for the treatment of moderate-to-severe OUD in patients who have undergone induction with a transmucosal buprenorphine-containing product to suppress opioid withdrawal signs and symptoms.
- RBP-6000 was designed to overcome some limitations of transmucosal buprenorphine products, which include the requirement of daily medication adherence, potentially sub-therapeutic plasma buprenorphine concentrations over the daily dosing interval, need for supplemental buprenorphine, and the potential for abuse, misuse, diversion, and accidental pediatric exposure.
- RBP-6000 is available in dosage strengths of 100-mg and 300-mg buprenorphine. RBP-6000 is injected SC as a solution, and subsequent precipitation of the polymer creates a solid depot containing the buprenorphine. After initial formation of the depot, buprenorphine is released via diffusion from, and the biodegradation of, the depot.
- The recommended dosing regimen for RBP-6000 is 300 mg every month for the first 2 months followed by either 100 mg or 300 mg monthly, based upon the patient's clinical condition.
- RBP-6000 is to be administered monthly by a HCP in a healthcare setting.

3.1 Proposed Indication

The proposed indication for RBP-6000 is treatment of moderate-to-severe OUD in patients who have undergone induction with a transmucosal buprenorphine-containing product to suppress opioid withdrawal signs and symptoms and to ensure tolerability to buprenorphine. RBP-6000 should be used as part of a complete treatment plan to include counselling and psychosocial support. RBP-6000 was designed to be used without the need for supplemental buprenorphine.

3.2 Treatment Administration and Dosing Regimen

RBP-6000 will be supplied in prefilled syringes (Figure 4) intended for monthly administration by SC injection by a HCP in a healthcare setting, and distributed through a restricted distribution system (see Section 7.3 for more information on the proposed product distribution). RBP-6000 is injected as a solution and should be administered SC in the abdominal region using the syringe and safety needle included with the product.

Figure 4: RBP-6000 Prefilled Syringe

RBP-6000 uses the ATRIGEL Delivery System, which consists of a biodegradable polymer, 50:50 poly(DL-lactide-co-glycolide) with a carboxylic acid end group (PLGH), dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). RBP-6000 contains 18% buprenorphine by weight. After initial formation of the depot, buprenorphine is released via diffusion from, and by the biodegradation of, the depot.

The ATRIGEL Delivery System is well-characterized and is currently used in the following 7 products approved worldwide, including the US: 4 formulations of Eligard® (leuprolide acetate injectable suspension) for the palliative treatment of advanced prostate cancer, Atridox® (doxycycline hyclate applied to the periodontal pocket) for the treatment of periodontal disease, Atrisorb® (Freeflow Bioabsorbable Guided Tissue Regeneration Barrier) for periodontal application, and Atrisorb®-D Barrier (Atribsorb with doxycycline) for periodontal guided tissue regeneration.

RBP-6000 is available in 100-mg and 300-mg doses. The approximate delivered volume is 0.5 mL and 1.5 mL for the 100-mg and 300-mg doses, respectively.

The recommended dosing regimen for RBP-6000 is 300 mg every month for the first 2 months followed by maintenance treatment of 100 mg or 300 mg every month, based upon the patient's clinical condition. Pharmacokinetic simulations indicate that an occasional delay in dosing up to 2 weeks is not expected to have a clinically significant impact on treatment effect. A subject who misses a dose should receive the next dose as soon as possible. Because of RBP-6000's long apparent half-life, doses should be administered at least 26 days apart.

If a situation arises where the depot needs to be removed, it must be surgically extracted. The depot is most easily removed within 14 days post-injection. Patients who elect to discontinue treatment with RBP-6000 should be monitored for several months for signs and symptoms of withdrawal and treated appropriately. Model simulations indicate that steady-state buprenorphine plasma concentrations decreased slowly over time following the last injection and remained, on average, above 2 ng/mL for 2 to 5 months depending on the dosage administered (100 mg or 300 mg, respectively).

Details on dose selection can be found in Section 4.4.

3.3 Mechanism of Action

The active pharmaceutical ingredient in RBP-6000 is buprenorphine free base. Buprenorphine is a partial agonist at the μ-opioid receptor, an antagonist at kappa- and delta-opioid receptors, and an agonist at the nociceptin/orphanin FQ (N/OFQ) receptor. The reinforcing, physical dependence-producing, and physiological effects of opioids depend on the activation of μ-opioid receptors. As a partial agonist, the effects of buprenorphine in nontolerant individuals are dose-dependent within a limited range, above which increasing dosages do not produce corresponding increases in effect. Thus, for certain pharmacologic effects (e.g., respiratory depression and sedation), buprenorphine may exhibit an enhanced safety profile compared with μ-opioid full agonists.

3.4 Objectives of Clinical Development Program

Based on limitations and challenges with current treatments for OUD, the objectives of development of RBP-6000 were to:

- Achieve opioid blockade starting from the first dose across the entire dosing interval at plasma concentrations of buprenorphine that are safe and well tolerated
- Provide a monthly treatment option that reduces the burden of daily treatment adherence that can be used without the need for rescue medications or supplemental buprenorphine
- Achieve clinically significant control of craving and withdrawal symptoms
- Reduce illicit opioid use
- Limit the possibility of diversion, misuse, abuse, and accidental pediatric exposure

3.5 Clinical Studies

The clinical development program for RBP-6000 consisted of the studies listed in Table 2. The opioid blockade study was conducted prior to the design of the Phase 3 studies to provide further evidence for dosage choices. The FDA indicated that the opioid blockade study could be used as a confirmatory study, such that only 1 adequate and well-controlled study demonstrating compelling results would be needed to demonstrate efficacy.

All studies enrolled subjects with a diagnosis of opioid dependence (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision [DSM-IV-TR]), or moderate or severe OUD (DSM-5). The data cut-off date for the RBP-6000 New Drug Application (NDA) was 12 August 2016. All relevant safety data from the recently concluded Phase 3 open-label (Ph3OL) study that were available as of the data cut-off date (12 August 2016) are included in this document. In addition, a long-term treatment extension study was initiated after the NDA data cut-off date.

Table 2: Clinical Studies in the RBP-6000 Development Program

Study Descriptor/ Number	Induction/ Dose Stabilization Phase [a]	Treatment Regimen, mg × doses (Number of Subjects Evaluated for Safety)	Duration of RBP-6000 Treatment	Subject Population
Phase 3				
Ph3DB: 13-0001	SUBOXONE SL film Induction/dose stabilization: up to 14 days Titrated up to 8 to 24 mg	RBP-6000 300 × 6 (N=201) RBP-6000 300 × 2 then 100 × 4 (N=203) Placebo × 6 (N=100)	24 weeks (6 SC injections)	OUD (DSM-5) Treatment-seeking
Ph3OL: 13-0003	SUBOXONE SL film Induction/dose stabilization: up to 14 days Titrated up to 8 to 24 mg	Roll-over [b]: RBP-6000 300→ 300 × 1 then flex × 5 (N=113) RBP-6000 100→ 300 × 1 then flex × 5 (N=112) Placebo→ 300 × 1 then flex × 5 (N=32) De novo [b] RBP-6000 300 × 1 then flex × 11 (N=412)	Roll-over: 24 weeks (6 SC injections) De novo: 48 weeks (12 SC injections)	OUD (DSM-5) Treatment-seeking
Phase 2				
MAD: 12-0005	SUBUTEX SL tablet Induction/dose stabilization: 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 × 4 (N=15) Cohort 2: 100 × 4 (N=15) Cohort 3: 200 × 4 (N=15) Cohort 4: 100 × 4 (N=15) Cohort 5: 200 × 4 (N=15) Cohort 6: 300 × 6 (N=14)	≥ 4 injections (≥ 16 weeks)	Opioid-dependent (DSM-IV-TR) Treatment-seeking
OB: 13-0002	SUBOXONE SL film Induction/dose stabilization: 13 to 14 days Titrated up to 8 to 24 mg	RBP-6000 300 × 2 (N=39)	8 weeks (2 SC injections)	OUD (DSM-5) **Not** treatment-seeking
Phase 1				
SAD: 11-0020	SUBOXONE SL tablet Induction/dose stabilization (Cohort 4 only): 7 days Titrated up to 12 mg	RBP-6000 Single dose Cohort 1: 50 (N=12) Cohort 2: 100 (N=12) Cohort 3: 200 (N=12) Cohort 4: 100 (N=12)	4 weeks (1 SC injection)	Opioid-dependent (DSM-IV-TR) Treatment-seeking
MW: 13-0006	SUBOXONE SL film Induction/dose stabilization 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)	OUD (DSM-5) Treatment-seeking

Study Descriptor/ Number	Induction/ Dose Stabilization Phase [a]	Treatment Regimen, mg × doses (Number of Subjects Evaluated for Safety)	Duration of RBP-6000 Treatment	Subject Population
FTIH: 10-0011	None	RBP-6000 Single dose 20 (N=12)	4 weeks (1 SC injection)	Opioid-dependent (DSM-IV-TR) Methadone treatment-seeking

MAD: multiple ascending dose, OB: opioid blockade, MW: molecular weight, FTIH: first-time-in-human

a. Doses are shown for buprenorphine.

b. Subjects who received RBP-6000 300-mg, RBP-6000 100-mg or placebo in Study 13-0001 and rolled over into Study 13--0003 received an initial dose of RBP-6000 300-mg in Study 13-0003. Thereafter, the RBP-6000 doses in Study 13-0003 may have been adjusted down to 100-mg and back up to 300-mg based on the medical judgment of the investigator (i.e., flex dosing).

4 CLINICAL PHARMACOLOGY

Summary

- The RBP-6000 clinical development program was based on the relationships between buprenorphine pharmacokinetics (PK), whole brain μ-opioid receptor occupancy (μORO), opioid blockade and clinically relevant efficacy endpoints.
- Prior published studies have shown that most individuals require ≥ 70-80% μORO to block the subjective effects of opioid agonists (otherwise known as opioid blockade), which corresponds to a buprenorphine plasma concentration of approximately ≥ 2-3 ng/mL.
- Transmucosal buprenorphine may not sustain plasma concentrations ≥ 2 ng/mL or μORO ≥ 70% over the 24-hour dosing interval. RBP-6000 was designed to overcome these limitations without the need for supplemental buprenorphine.
- Clinical pharmacology data on RBP-6000 come from 7 clinical studies.
- RBP-6000 300 mg achieves buprenorphine plasma levels that provide opioid blockade starting from administration of the first dose across the dosing interval. On this basis, a 300-mg dosing regimen was evaluated in the Phase 3 double-blind (Ph3DB) study.
- Monthly doses of RBP-6000 100-mg also achieved targeted buprenorphine plasma levels at steady-state. A regimen of 2 monthly injections of 300-mg followed by 4 monthly injections of 100-mg was the second dosing regimen evaluated in the Ph3DB study, with the 2 initial 300-mg doses being given to achieve targeted plasma levels more rapidly.

4.1 Background

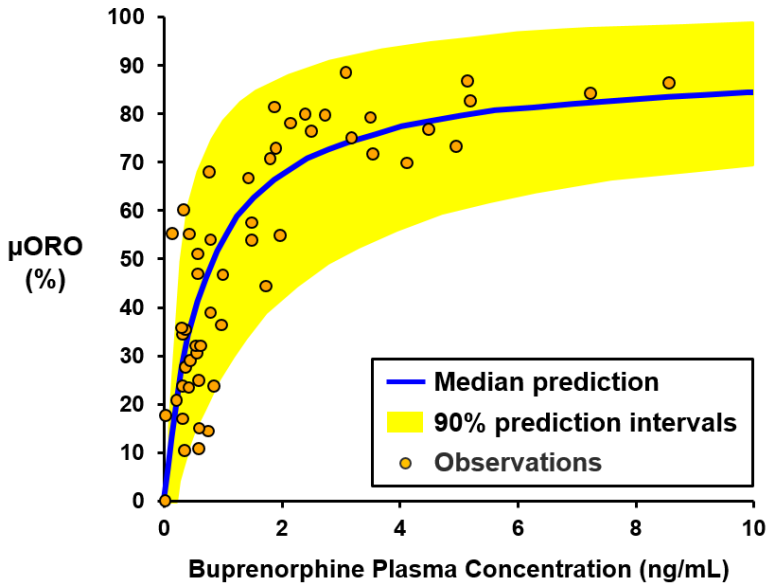
The clinical program for RBP-6000 was based on the scientific understanding of the relationships between buprenorphine plasma concentration, whole brain μORO (measured using positron emission tomography [PET]), and blockade of subjective opioid effects.

The primary data come from two studies that evaluated the relationship between brain μORO and the pharmacodynamic (PD) effects of buprenorphine. In the first study, subjects were sequentially maintained on SL buprenorphine doses of 32 mg, 16 mg, 2 mg, and placebo (Greenwald et al. 2003). PET scans were conducted at 4 hours post-dose. In the second study, subjects were maintained on 16 mg SL buprenorphine, and PET scans were conducted at 4, 28, 52, and 76 hours after the last buprenorphine dose (Greenwald et al. 2007). In both studies, hydromorphone challenges were given to assess the ability of buprenorphine to block the effects of a μ-opioid full agonist.

Pooled data from these 2 studies suggested that at least 70% μORO was required to achieve opioid blockade, i.e., the suppression of the subjective effects of a μ-opioid full agonist (Nasser et al. 2014). Figure 5 illustrates the median prediction and 90% prediction intervals for the relationship between μORO and buprenorphine plasma concentration. The results demonstrate that μORO increases with buprenorphine concentration until a plateau is reached, which is

consistent with the saturation of μ-opioid receptors in the brain. These data suggested that the plasma concentration of buprenorphine needed to achieve ≥ 70% μORO was approximately ≥ 2 ng/mL.

Figure 5: Relationship between Whole Brain μORO and Buprenorphine Plasma Concentration (Nasser 2014)



In summary, the totality of the data from the literature suggested the following:

- Withdrawal suppression appears to require ≥ 50% μORO, which is associated with buprenorphine plasma concentrations ≥ 1 ng/mL.
- Opioid blockade (i.e., blockade of the reinforcing and subjective effects of typical doses of abused opioids) appears to require ≥ 70-80% μORO, which is associated with buprenorphine plasma concentrations ≥ 2-3 ng/mL.
- A higher degree of μORO, and thus higher buprenorphine concentrations, to achieve opioid blockade may also be required based on factors such as genetics, concomitant medical conditions (e.g., chronic pain, hepatic disease), psychiatric conditions, comorbid abuse of non-opioid substances (e.g., nicotine, cocaine), and abuse of high doses of opioids.

4.2 Overview of Clinical Pharmacology Program

The clinical pharmacology and PK of RBP-6000 were evaluated in 7 clinical studies in subjects with OUD to assess single- and multiple-dose PK and exposure-response relationships for achieving efficacy (Table 2).

PK modeling was implemented early in the development program to characterize the PK of RBP-6000 after a single dose (using single ascending dose [SAD] study data) and multiple doses

(using the MAD study data) and to predict whole brain μORO (see Section 4.3.1). This model-based approach provided the criteria for dose selection in the Phase 2 and Phase 3 programs. A combined population PK model was developed using data from the MAD study, the Ph3DB study, and the Ph3OL study (see Section 4.3.3).

4.3 Pharmacokinetic Characteristics

4.3.1 *Phase 1/2 SAD and MAD Studies*

Following single SC administration of 50, 100, and 200 mg RBP-6000 in opioid-dependent subjects (SAD Study), the apparent clearance of buprenorphine was approximately 65 L/hr over the dose range. The shape of the PK curves for all doses had an initial peak at around 24 hours post-dose followed by a decline in plasma concentrations to a plateau throughout the dosing interval, consistent with the slow release of buprenorphine from the SC depot. A second peak could be observed in some subjects at around 6 to 11 days post-dose. The apparent terminal plasma half-life of buprenorphine ranged between 43 to 60 days.

The PK of RBP-6000 was investigated after repeated (≥ 4) SC injections at doses of 50, 100, 200, and 300 mg separated by 28 days in the MAD study (Study 12-0005). After 4 SC injections (Day 85), a 6-fold increase in dose resulted in a 5.1-fold increase in buprenorphine maximum plasma concentration (C_{max}; 1.84 to 9.38 ng/mL) and a 5.2-fold increase in the area under the plasma concentration-time curve over the dosing interval (AUC_{tau}; 623 to 3216 ng*hr/mL). Buprenorphine clearance was fairly constant over the investigated dose range (80-103 L/hr). The time to C_{max} (T_{max}) ranged between 20 to 24 hours across all dose levels.

Section 4.4 describes how these data were used to select doses for further investigation in Phase 3.

4.3.2 *Effect of Intrinsic Factors*

The effects of age, sex, race, and body mass index (BMI) on buprenorphine exposure were evaluated in the combined population PK analysis as detailed in Section 4.3.3.

The effect of hepatic impairment on the PK of RBP-6000 was not specifically evaluated; however, the effect of hepatic impairment on the PK of buprenorphine has been evaluated using SUBOXONE SL tablets (2 mg/0.5 mg buprenorphine/naloxone). No clinically relevant changes were observed in subjects with mild hepatic impairment. Buprenorphine plasma exposure (AUC_{last}) increased by 64% and 181% in subjects with moderate and severe impairment, respectively, compared to healthy subjects (SUBOXONE Prescribing Information February 2017). Because RBP-6000 cannot be titrated, subjects with severe hepatic impairment are not candidates for treatment with RBP-6000. Patients who develop moderate-to-severe hepatic impairment while being treated with RBP-6000 should be monitored for signs and symptoms of toxicity or overdose caused by the increased levels of buprenorphine.

Systemic clearance is not expected to be related to renal function since buprenorphine clearance is considered to occur mainly by hepatic metabolism. Less than 1% is excreted as unchanged buprenorphine in urine following IV buprenorphine administration (SUBOXONE Prescribing

Information February 2017). Creatinine clearance was not a significant covariate in the combined population PK analysis (Section 4.3.3).

The effects of CYP3A4 inhibitors on buprenorphine exposure in subjects treated with RBP-6000 have not been evaluated in a dedicated drug-drug interaction study. However, the interaction between ketoconazole and SUBUTEX tablets has been investigated. Co-administration of ketoconazole with SUBUTEX resulted in a 2-fold increase in mean buprenorphine exposure (AUC) (Report #1974508 2001). This increase is attributed to both the inhibition of buprenorphine systemic clearance and the inhibition of the first-pass metabolism since a fraction of the SL-administered drug is swallowed. The existence of first-pass metabolism for SL buprenorphine is supported by the observation of a much higher norbuprenorphine (primary metabolite of buprenorphine)-to-buprenorphine AUC ratio following SL administration (1.57) compared to RBP-6000 SC injection (0.30) and IV buprenorphine (0.18).

A drug-drug interaction population PK model was developed to account for this first-pass metabolism for SL buprenorphine and to predict the effect of ketoconazole (strong CYP3A4 inhibitor) on the PK of buprenorphine following SC administration of RBP-6000, which bypasses first-pass metabolism. The model predicted a moderate 60% increase in buprenorphine area under the curve (AUC) with concomitant administration of ketoconazole. In addition, data from 29 subjects receiving CYP3A4 inhibitors concomitantly with RBP-6000 in the Ph3DB study did not reveal any trend of increase in buprenorphine plasma concentrations. Taken together, these data support the absence of any clinically meaningful increase in buprenorphine exposure following SC injection of RBP-6000 and concomitant administration of CYP3A4 inhibitors.

Co-administration of CYP3A4 inducers may induce the metabolism of buprenorphine and, therefore, may cause an increase in the clearance of the drug, potentially leading to a decrease in buprenorphine plasma concentrations. The effects of CYP3A4 inducers may be dependent on the route of administration of buprenorphine. Buprenorphine is a high extraction ratio drug (hepatic extraction ratio, 0.6 - 0.9). Hence, elimination is expected to be hepatic blood flow-dependent and relatively insensitive to changes in intrinsic clearance (i.e., hepatic metabolism) (Bruce et al. 2006). Since RBP-6000 is injected SC, the induction of CYP3A4 enzymes is expected to result in minimal decrease in buprenorphine exposure.

4.3.3 *Population PK Modeling*

Robust population PK models have been developed to characterize the PK of buprenorphine following SC injections of RBP-6000. A 2-compartment disposition model with first-order elimination was selected, together with a dual-absorption model to account for the rapid absorption process associated with the early peak and the slow release of buprenorphine from the SC depot. This model adequately described buprenorphine plasma concentration data in a large number of subjects (570 subjects in the MAD, Ph3DB, and Ph3OL studies; total of 19,686 observations) and over multiple SC injections (up to 12 injections covering a 1-year exposure) for doses ranging between 50 to 300 mg. The model confirmed that steady-state was reached

after 6 SC injections, supported dose proportionality, and indicated that re-injection of RBP-6000 in the same abdominal quadrant had no impact on buprenorphine plasma exposure.

Model simulations were conducted to assess the impact of an occasional delay in dosing and treatment interruption. Simulations showed that an occasional 2-week delay in dosing had only minor impact on buprenorphine concentrations and predicted levels of brain μORO, suggesting loss of efficacy is unlikely under these circumstances. After the last SC injection, buprenorphine plasma concentrations were predicted to decrease slowly over time and to remain, on average, above 2 ng/mL for 2 to 5 months on average, depending on the dosage administered (100 mg or 300 mg, respectively).

Inter-individual variability in demographics, drug-metabolizing enzymes, and laboratory data was also evaluated. Two statistically significant covariates were identified: sex and BMI. Sex had a significant effect on the slow absorption rate of buprenorphine from the depot, but this effect was marginal (+7.6% in females) and was not clinically significant. BMI (ranging from 18 to 35 kg/m^2) was also found to affect SC absorption and apparent clearance (CL/F) of buprenorphine, with higher exposure levels in subjects with a lower BMI. However, these differences were not of sufficient magnitude to suggest that dose adjustments are necessary (~15% increase in median exposure and ~33% increase in median C_{max} for subjects in the lower BMI quartile compared to subjects in the upper BMI quartile). These determinations are supported by similar safety profiles as well as subgroup analyses of the primary efficacy endpoint in the Ph3DB study, which showed similar efficacy by dosing regimen across the BMI range and by sex (see Section 5.1.4.3).

4.4 Studies Supporting Dose Selection for Phase 3 Studies

4.4.1 *SAD and MAD Studies*

Data from the SAD and MAD studies, as well as information from prior studies on the relationship between buprenorphine plasma concentration and whole brain μORO (Greenwald et al. 2003; Greenwald et al. 2007), were used to identify the dosing regimens for Phase 3. A brief summary of the results is provided below:

- **RBP-6000 300-mg** would achieve an average buprenorphine plasma concentration ~2 ng/mL after the first dose, which would be associated with approximately 70% μORO. Subsequent monthly doses would provide sustained average plasma concentrations above 2-3 ng/mL, the buprenorphine levels associated with opioid blockade in prior studies. It was estimated that steady-state levels would be reached after 6 doses with an average buprenorphine plasma concentration of approximately 6 ng/mL.
- **RBP-6000 100-mg** would achieve average buprenorphine plasma concentrations above 2-3 ng/mL at steady-state after 6 monthly doses. It was determined that 2 initial consecutive monthly doses of 300-mg could be used to achieve buprenorphine target levels more quickly and maintain buprenorphine concentrations thereafter with monthly administration of 100-mg doses.

4.4.2 *Opioid Blockade Study (Study 13-0002)*

The opioid blockade study was a Phase 2 single-site study to assess the blockade of subjective opioid effects, buprenorphine PK, and safety of multiple SC injections of RBP-6000 in 39 subjects with moderate or severe OUD who were not treatment-seeking. The opioid blockade study was designed in consultation with the FDA to test the hypothesis based on the MAD study (Study 12-0005) data and PK/PD modeling results that monthly doses of 300 mg of RBP-6000 would block the effects of a μ-opioid full agonist (hydromorphone). Hydromorphone is a short-acting μ-opioid full agonist commonly used in human laboratory studies as a prototypic opioid agonist. This study also provided dose rationale for the pivotal efficacy study (Study 13-0001).

Figure 6 provides an illustration of the study design. Subjects were initially inducted on SUBOXONE sublingual film to reach a final buprenorphine dosage of 8 to 24 mg per day. Two doses of RBP-6000 300 mg were given at a 4-week interval on Day 1 and Day 29. To assess opioid blockade, subjects were challenged with placebo, 6 mg hydromorphone, or 18 mg hydromorphone given IM at various times during the study. Each time, challenges with hydromorphone/placebo were administered in a randomized sequence on 3 consecutive days such that all subjects experienced each of the 2 hydromorphone challenges or placebo in a blinded fashion. Hydromorphone challenge sessions were performed at Screening (Day -17 to Day -15), during SUBOXONE film treatment (Day -3 to Day -1), and then every week following each SC injection of RBP-6000 300 mg up to 8 weeks after the second and last dose. The primary outcome measure was the Drug Liking VAS (“Do you like the drug?”) measured on a 0-100 mm unipolar VAS scale where 0 indicated “not at all” and 100 indicated “extremely”.

Figure 6: Opioid Blockade Study Design

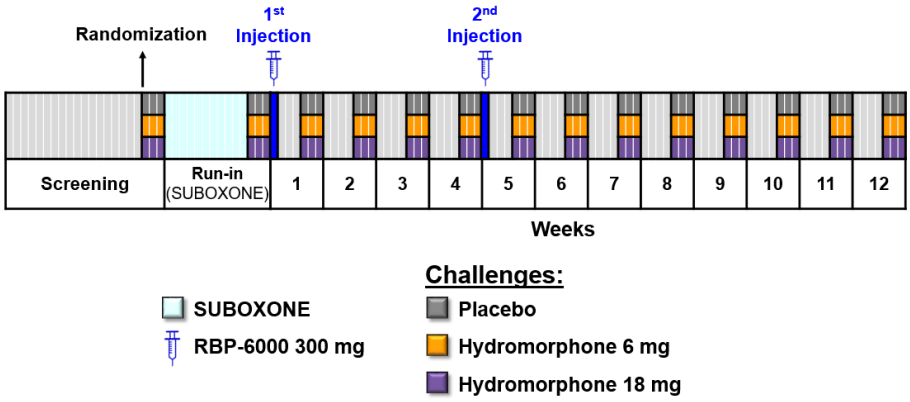


Figure 7 provides an illustration of the mean buprenorphine plasma concentration curve from the opioid blockade study. The gray shaded region reflects the PK profile during the SUBOXONE sublingual film induction/run-in period, which was characterized by the expected daily variability in peak and trough levels. The PK profile of RBP-6000 300 mg after the first injection is reflected in an early peak followed by sustained release with mean buprenorphine plasma concentrations of approximately 2 ng/mL throughout the monthly dosing interval. Following the second injection, mean plasma concentrations were maintained in the range of approximately 3-4 ng/mL for two months.

Figure 7: Mean Buprenorphine Plasma Concentrations from Opioid Blockade Study

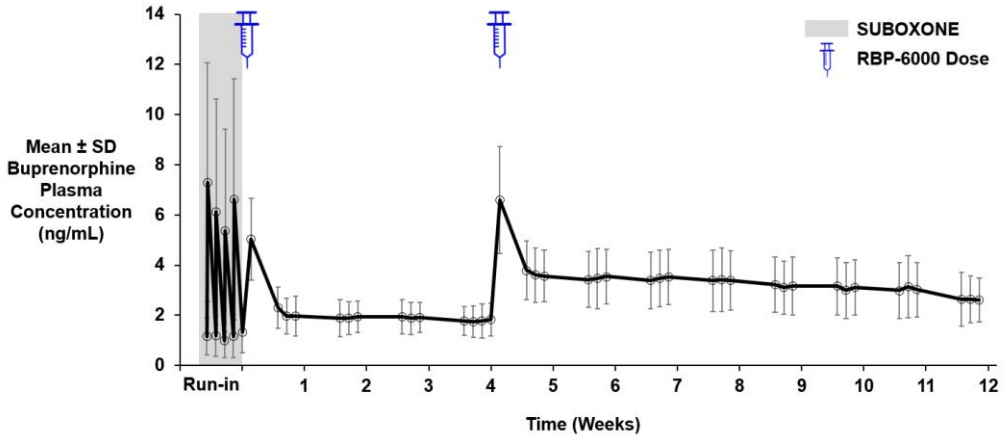
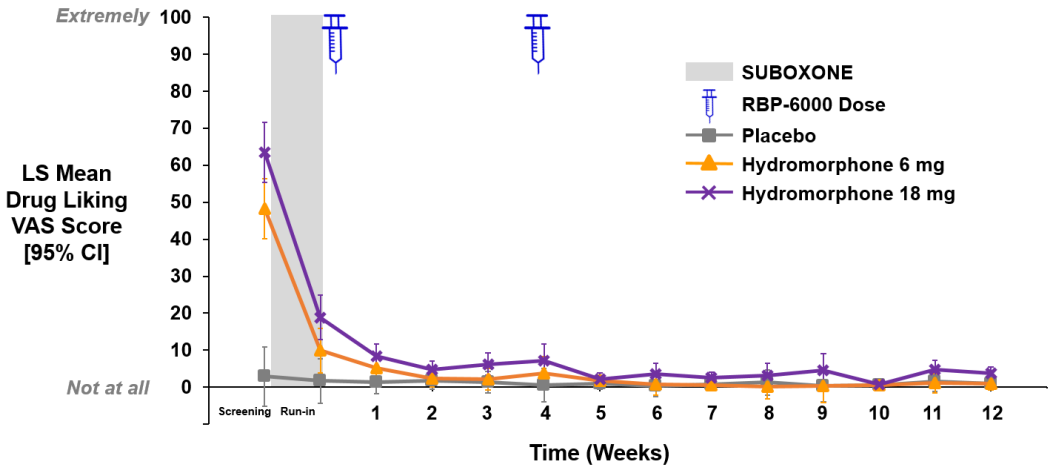


Figure 8 illustrates the least squares (LS) mean Drug Liking VAS scores. At baseline (prior to subjects receiving either SUBOXONE or RBP-6000), subjects reported considerable liking for both hydromorphone 6 mg and 18 mg, with mean values of 49 mm and 65 mm on the 0-100 mm scale. After treatment with SUBOXONE sublingual film, decreases in Drug Liking VAS scores were observed but not opioid blockade, as evidenced by mean scores of 10 mm and 19 mm for the 2 respective hydromorphone challenges. After the first injection of RBP-6000 300 mg, mean scores were consistently below 10 mm and the median score ranged between 0 and 2 mm for both hydromorphone challenges across study visits, demonstrating that RBP-6000 300 mg provided opioid blockade from the first dose.

Figure 8: Mean Drug-Liking VAS Scores from Opioid Blockade Study (Study 13-0002)



From a subject-level perspective, 3 (8%) of the 38 subjects did not have consistent reductions in Drug Liking after treatment with RBP-6000. These 3 subjects had buprenorphine plasma concentrations that were consistent with the overall study PK profile (i.e., ~2 ng/mL). This finding was not unexpected given that some individuals are known to require concentrations >2-3 ng/ml to achieve opioid blockade (Greenwald et al. 2014).

Overall, the opioid blockade study demonstrated that RBP-6000 300 mg could provide opioid blockade after the first dose of treatment. The study provides support for the rationale of the dosing regimens in the Ph3DB study, which initiated treatment with 2 doses of 300 mg.

4.4.3 *Rationale for Phase 3 Dosing Regimens*

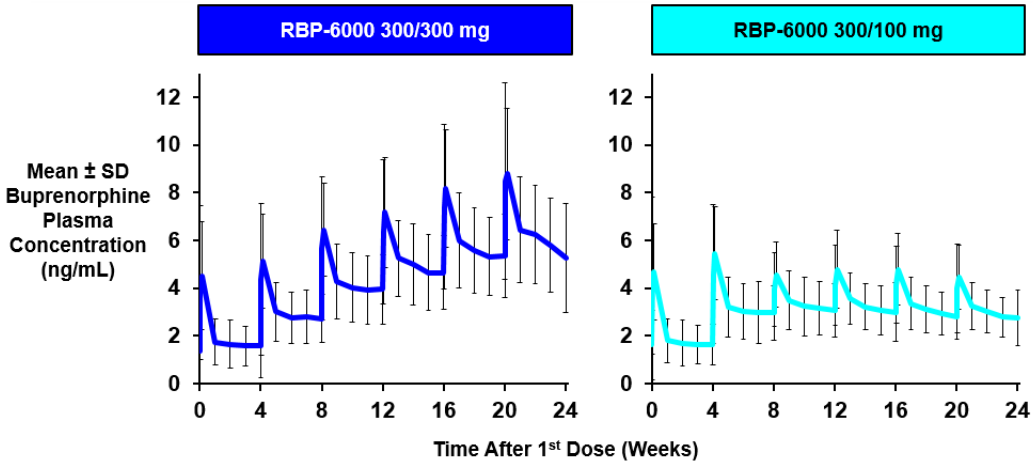
The totality of results from the SAD study, MAD study, and opioid blockade study provided support for the dosing regimens selected for the Phase 3 program. In terms of safety, the Phase 1 and Phase 2 studies indicated that the safety and tolerability profile of RBP-6000 100 mg and 300 mg were similar to that of current transmucosal products and there were no unexpected findings. In terms of efficacy, the rationale for the dosing regimens is provided below:

- RBP-6000 300 mg was selected for the Phase 3 dosing regimens because it provided opioid blockade from the first dose of treatment, as shown in the opioid blockade study.
- **RBP-6000 300/100 mg** (two SC injections of 300 mg followed by 4 SC injections of 100 mg) – data suggested that monthly 100-mg doses could maintain buprenorphine concentrations associated with opioid blockade (≥ 2-3 ng/mL) following 2 initial doses of 300 mg
- **RBP-6000 300/300 mg** (6 SC injections of 300 mg) – data suggested that repeated monthly doses of RBP-6000 300 mg could provide buprenorphine concentrations above target levels of 2-3 ng/mL, consistent with the required exposures that the literature suggests are required for patients with certain clinical conditions to achieve opioid blockade

4.5 Pharmacokinetics of Phase 3 Dosing Regimens

Figure 9 illustrates the mean buprenorphine plasma concentrations for the 2 RBP-6000 dosing regimens in the Ph3DB study (> 11,000 PK samples). The figure illustrates that the PK profiles of both dosing regimens were consistent with Phase 1 and Phase 2 data as well as with PK model expectations. Higher buprenorphine concentrations with the 300/300-mg regimen compared with the 300/100-mg regimen were evident particularly at the end of the study since the 300/100-mg regimen included 2 initial 300-mg doses followed by 4 monthly doses of 100-mg.

Figure 9: Mean Buprenorphine Plasma Concentrations from Ph3DB Study



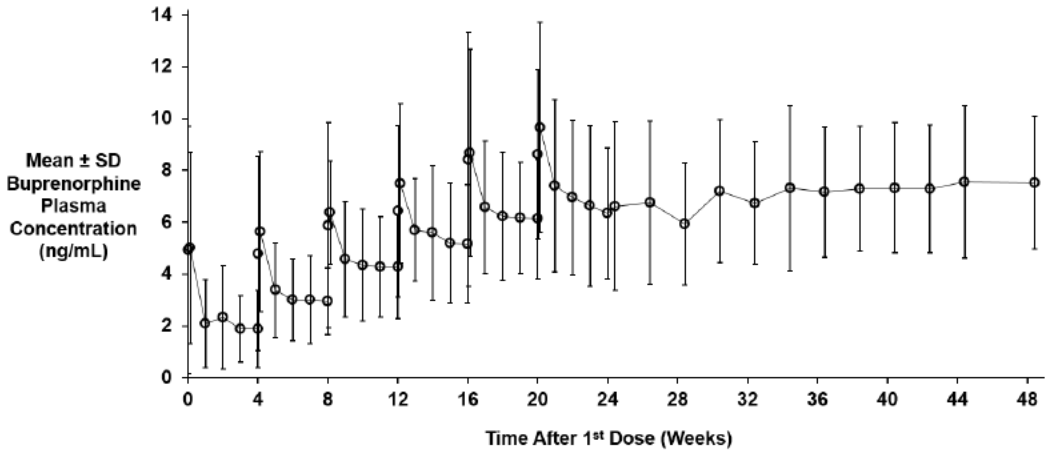
Estimated mean average, minimum and maximum buprenorphine plasma concentrations for 100-mg and 300-mg doses of RBP-6000 after 6 injections are provided in Table 3.

Table 3: Estimated Mean Buprenorphine 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

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

Steady-state buprenorphine concentrations are reached after the 6th dose of RBP-6000. Figure 10 illustrates the mean buprenorphine plasma concentration among subjects who received 300-mg doses for 12 consecutive monthly injections in the Ph3DB and Ph3OL studies, where the steady-state profile after 6 months is more evident. (Note: PK sampling prior to Week 24 (Ph3DB study) is more frequent than after Week 24 (Ph3OL study).

Figure 10: Mean Buprenorphine Plasma Concentrations among Subjects Receiving 12 Consecutive Monthly 300-mg Doses



5 PHASE 3 CLINICAL EFFICACY

Summary

- The pivotal Phase 3 study was a randomized, double-blind, placebo-controlled trial in 504 MAT-seeking subjects with OUD.
- Two monthly RBP-6000 dosing regimens were evaluated in the Ph3DB study:
  - 300/300 mg: RBP-6000 300-mg × 6 doses
  - 300/100 mg: RBP-6000 300-mg × 2 doses, then RBP-6000 100-mg × 4 doses
- All subjects in the study received standardized IDC in addition to their randomized assignment.
- After randomization, the use of supplemental buprenorphine was not allowed.
- The percentage of subjects completing the Ph3DB study was significantly higher in the RBP-6000 groups compared to the placebo group.
- The primary efficacy endpoint (percentage abstinence between Weeks 5 and 24) and key secondary efficacy endpoint (≥ 80% abstinence between Weeks 5 and 24) in the Ph3DB study were met, demonstrating superiority of both RBP-6000 dosage regimens over placebo.
- Other secondary efficacy endpoints including opioid craving, withdrawal symptoms, and clinical improvement, substantiated the benefits observed in the primary and key secondary efficacy endpoints.
- The proportion of subjects employed increased during the treatment period in the RBP-6000 groups and declined in the placebo group.
- Subgroup analyses were consistent with prior literature suggesting that some individuals (e.g., injecting drug users) may benefit from higher doses of buprenorphine.
- The Ph3OL study found that the efficacy of RBP-6000 was maintained through 12 monthly doses.

5.1 Pivotal Phase 3 Double-Blind Study (Study 13-0001)

5.1.1 *Study Design*

The Ph3DB study was a randomized, double-blind, placebo-controlled, multicenter clinical trial designed to assess the efficacy, safety and tolerability of multiple monthly SC injections of RBP-6000 in treatment-seeking subjects with a diagnosis of moderate or severe OUD (DSM-5). The primary objective was to assess the efficacy of RBP-6000 compared to placebo in treatment-seeking individuals with OUD.

The Ph3DB trial design was discussed in collaboration with, and incorporated feedback from, the FDA. Several trial designs were considered including an active-controlled non-inferiority trial against transmucosal buprenorphine. Ultimately, it was determined that a placebo-controlled

superiority trial was most appropriate to provide support for marketing approval of RBP-6000. First, appreciable amounts of missing data, which are to be expected in OUD treatment studies, can threaten the validity of non-inferiority trials, since more missing data can bias the result towards demonstrating non-inferiority (Wiens et al. 2013). Furthermore, an active-controlled trial with transmucosal buprenorphine would have required the use of a double-dummy technique where subjects receiving monthly doses of RBP-6000 and weekly IDC would also have also had to take a daily placebo treatment. Because the primary goal was to study the efficacy of RBP-6000 as it will be used in clinical practice (i.e., monthly dosing + IDC) and the potential effects of using a daily placebo on top of monthly treatment were unknown, it was determined that a placebo-controlled superiority trial was an appropriate design.

The study inclusion criteria allowed for enrollment of subjects aged 18 to 65 years who were generally healthy with a diagnosis of moderate or severe OUD per DSM-5. All subjects were seeking MAT and none could have taken MAT for OUD within the previous 90 days. Subjects were excluded if they had other diagnoses requiring opioids, recent history of suicidality, or significant medical problems. A full list of inclusion and exclusion criteria are included in Appendix 10.1.

Figure 11 provides an overview of the design of the Ph3DB study. Following an initial screening period of up to 2 weeks, subjects entered a run-in period and were inducted on SUBOXONE sublingual film at a daily dose up to 24 mg buprenorphine. The purpose of the 2-week SUBOXONE run-in period was to ensure that subjects who had not been on MAT for at least 90 days could tolerate buprenorphine (e.g., no hypersensitivity) and to ensure that buprenorphine could suppress withdrawal symptoms prior to receiving a monthly injection. Importantly, induction with a transmucosal buprenorphine-containing product prior to receiving RBP-6000 is consistent with the proposed indication for use.

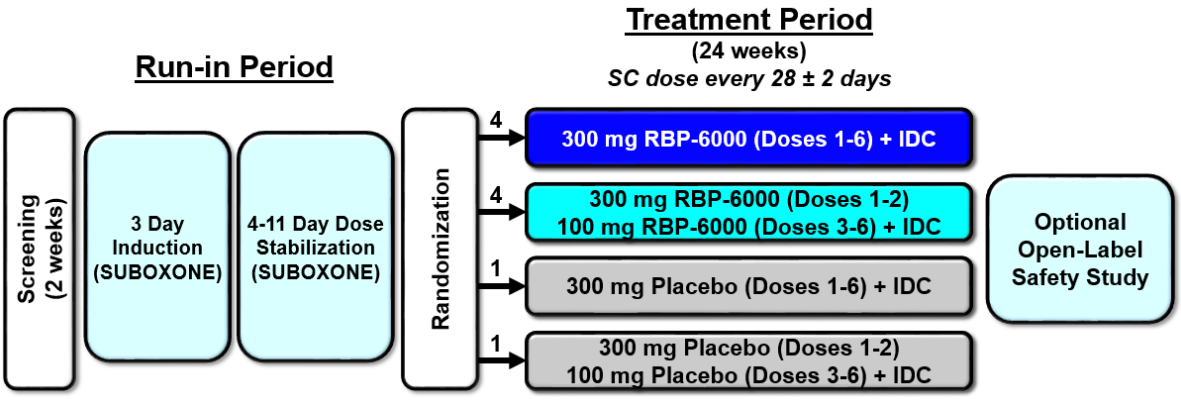
If subjects had adequate control of withdrawal symptoms and opioid craving (i.e., Clinical Opiate Withdrawal Scale [COWS] scores indicative of no or mild signs/symptoms [≤ 12] and an Opioid Craving VAS score of ≤ 20 mm on a 100-mm scale) following run-in on SUBOXONE sublingual film, subjects were randomized to treatment groups in a 4:4:1:1 ratio to the following treatment regimens (note: placebo was the ATRIGEL Delivery System without buprenorphine):

- **RBP-6000 300/300-mg:** RBP-6000 300-mg SC every 28 days (± 2) × 6 doses + IDC
- **RBP-6000 300/100-mg:** RBP-6000 300-mg SC every 28 days (± 2) × 2 doses followed by RBP-6000 100-mg SC every 28 days (± 2) × 4 doses + IDC
- **Placebo 300/300-mg:** Placebo 300-mg SC every 28 days (± 2) × 6 doses + IDC
- **Placebo 300/100-mg:** Placebo 300-mg SC every 28 days (± 2) × 2 doses followed by placebo 100-mg SC every 28 days (± 2) × 4 doses + IDC

In addition to study treatment, all randomized subjects received IDC at least once per week starting at Day 1 and continuing through the end of the study.

For the purposes of analysis, the 2 placebo regimens were pooled into a single placebo group as pre-specified in the statistical analysis plan (SAP).

Figure 11: Design of the Ph3DB Study



At the suggestion of the FDA, the Ph3DB study protocol was amended to include a 5-day SUBOXONE sublingual film taper to be initiated at Day 1 following the first injection of study treatment. The purpose of this taper was to facilitate preservation of the blind of the study, to mitigate withdrawal symptoms, and to facilitate retention of subjects treated with placebo. Specific ancillary medications (e.g., ibuprofen, acetaminophen, hydroxyzine) were allowed to alleviate symptoms of opioid withdrawal as necessary. Importantly, the use of supplemental buprenorphine was not allowed.

5.1.1.1 *Efficacy Endpoints*

Abstinence from opioids, the primary measure of efficacy, was assessed by results from weekly centrally tested urine drug screening (UDS) combined with weekly self-reported illicit opioid use. Investigational site staff and study subjects were blinded to UDS results, with the exception of Screening UDS results which were used to assess eligibility, and possible in-office benzodiazepine UDS for subject safety.

Self-reported illicit opioid use was collected using an in-person Timeline Followback (TLFB) interview. The TLFB interview (Fals-Stewart et al. 2000) is a method used to assess recent drug use and was administered electronically by an interviewer. The interview instrument asked subjects to retrospectively estimate their drug use in the 30 days prior to screening at the screening visit and since the last visit at all subsequent visits. Subjects reported either illicit use or no illicit use of opioids, methadone, buprenorphine, cocaine, barbiturates, benzodiazepines, amphetamines/methamphetamines, phencyclidine, and ethanol. The TLFB interview was completed at the screening visit and prior to study treatment injection, and was administered at approximately the same time each day ± 2 hours.

The primary efficacy endpoint in the Ph3DB study was percentage abstinence from Week 5 to Week 24 (i.e., the percentage of weeks in which the subject had a negative UDS and negative self-report for illicit opioid use [UDS + self-report] from Week 5 through Week 24). While the double-blind phase of the study was conducted from Week 1 to Week 24, the analysis of the

primary and key secondary efficacy endpoints began at Week 5. The use of a "grace period" (i.e., starting the efficacy period at Week 5) allowed subjects the opportunity to more fully engage in treatment.

The key secondary efficacy endpoint was treatment success, defined as any subject with ≥ 80% abstinence (UDS + self-report) from Week 5 through Week 24. Other secondary efficacy endpoints, exploratory endpoints and tertiary endpoints investigated are shown in Table 4.

Instruments Used for Other Secondary Endpoints:

- The Opioid Craving VAS measured the amount of opioid craving that a subject felt for illicit opioids along a 100-mm scale anchored by word descriptors at each end where 0 indicated "no craving" and 100 indicated "strongest craving ever." The Opioid Craving VAS was assessed prior to each injection, and weekly throughout the study.
- The COWS is an 11-item, validated instrument completed by clinicians to assess signs and symptoms of opiate withdrawal (Wesson 2003, Tompkins 2009). The score is the sum of the response to each of the 11 items. A score of 5 to 12 is considered mild, 13 to 24 is moderate, 25 to 36 is moderately severe and a score > 36 is considered severe withdrawal. The COWS was assessed prior to each injection, and weekly throughout the study.
- The Subjective Opiate Withdrawal Scale (SOWS) is a 16-item, subject-completed scale to assess opiate withdrawal symptoms. The instrument consists of 16 symptoms rated in intensity on a 5-point ordinal scale: 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely. The total score is a sum of item ratings and ranges from 0 to 64. The SOWS was assessed prior to each injection, and weekly throughout the study.

Table 4: Summary of Efficacy Endpoints in the Ph3DB Study

Endpoint	Statistical Method	Missing Data Approach
Primary Efficacy Endpoint		
Percentage abstinence (i.e., percentage opioid-free weeks) based on UDS + self-report (TLFB) from Week 5 through Week 24	Wilcoxon rank-sum test	Missing data were treated as positive for opioids
Key Secondary Efficacy Endpoint		
Treatment success, defined as any subject with ≥ 80% percentage abstinence (UDS + self-report) from Week 5 through Week 24	CMH test	Missing data were treated as positive for opioids
Additional Secondary Efficacy Endpoints		
Percentage of urine samples (UDS) negative for opioids from Week 5 through Week 24	Wilcoxon rank-sum test	Missing data were treated as positive for opioids
Percentage of self-reports negative for illicit opioid use collected from Week 5 through Week 24	Wilcoxon rank-sum test	Missing data were treated as positive for opioids
Percentage of completers[a]	CMH test	No imputation
Percentage of subjects abstinent (UDS + self-report)	CMH test	No imputation
Total number of weeks of abstinence (UDS + self-report) from Week 5 through Week 24	ANOVA	Missing data were treated as positive for opioids
Change from baseline in Opioid Craving VAS	MMRM	Model based
Change from baseline in total score on the COWS	MMRM	Model based
Change from baseline in total score on the SOWS	MMRM	Model based

ANOVA = analysis of variance; CMH = Cochran-Mantel-Haenszel; COWS = clinical opiate withdrawal scale; MMRM = mixed model for repeated measures; SOWS = subjective opiate withdrawal scale; VAS = visual analog scale
[a] A completer was defined as a subject who completed the Week 24 visit, with either UDS or self-report (TLFB) assessment.

5.1.1.2 *Statistical Analyses*

The primary analysis population was the Full Analysis Set (FAS), which was defined as any subject who was randomized and allocated study treatment, analyzed under the intention-to-treat (ITT) principle. The 2 randomized placebo groups were combined and analyzed as 1 group as pre-specified in the study protocol.

The primary efficacy endpoint (percentage abstinence) was based on visits in which paired urine samples and self-reports were expected for each subject, and the Wilcoxon rank-sum test was used to test for differences between treatment groups. Missing UDS samples and/or self-reports (including missing assessments from prematurely discontinued subjects) were imputed as positive for opioids. Subgroup analyses were performed for injecting vs. non-injecting opioid users based on baseline assessment, use of illicit opioids during run-in, age, sex, race, BMI, geography, severity of OUD, and duration of opioid use.

The key secondary endpoint, treatment success, was analyzed using the Cochran-Mantel-Haenszel (CMH) test. A parallel Bonferroni gatekeeping approach was used to control familywise error rate (α=0.05) for the primary and key secondary efficacy endpoints.

Change from baseline for the Opioid Craving VAS, COWS, and SOWS were evaluated using mixed-models for repeated measures (MMRM), a model frequently used for longitudinal data in

clinical trials with missing data. One limitation of the MMRM model is that the model assumes that missing data are "missing at random". The "missing at random" assumption, while untestable, is unlikely to be met for most of the cases of missingness in this study. Therefore, additional sensitivity analyses were performed on these endpoints to ensure the robustness of results to different assumptions underlying the missing data.

In agreement with the FDA, data from 1 site with 15 subjects (300/300 mg: n=5, 300/100 mg: n=9, placebo: n=1) were removed from the efficacy analyses (FAS) due to compliance issues; these subjects were included in safety analyses.

5.1.2 *Subject Disposition*

A total of 1187 subjects were screened, 665 subjects entered the open-label run-in phase, and 504 subjects were randomized into the study. A total of 201 subjects were randomized to the RBP-6000 300/300-mg group, 203 subjects to the RBP-6000 300/100-mg group, and 100 subjects to the placebo groups. Approximately two-thirds of subjects in both RBP-6000 groups completed the study compared to approximately one-third in the placebo group, and few subjects (≤ 5.0%) across groups discontinued due to treatment-emergent adverse events (TEAEs) (Table 5). The largest differences in reasons for discontinuation were lack of efficacy (18.0% in placebo group compared to 1.5% to 2.5% in the RBP-6000 groups) and withdrawal of consent (18% in placebo group compared to 9.9% and 10.4% in the RBP-6000 groups).

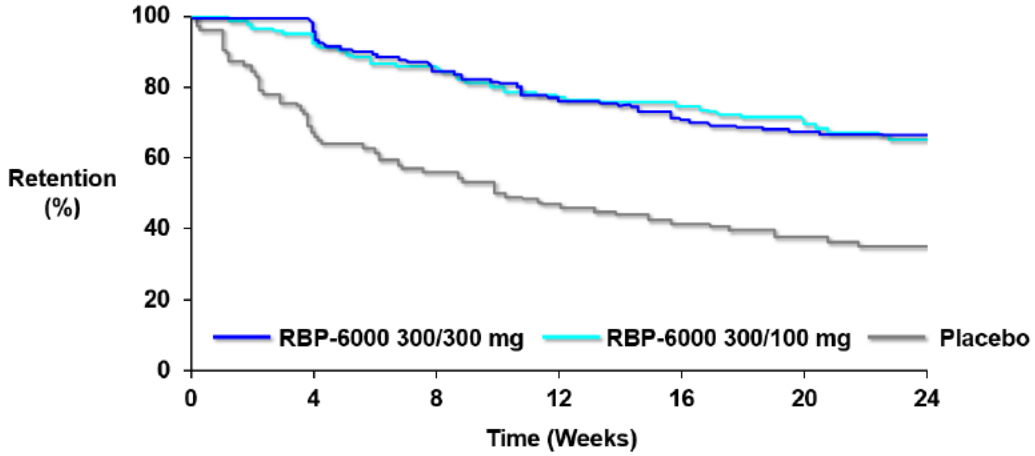
Table 5: Subject Disposition – All Randomized Subjects

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

[a] Discontinuation due to "other" includes site closed by sponsor, incarceration, relocation, and noncompliance.

The Kaplan-Meier estimates for retention in the study were higher for the 300/100-mg and 300/300-mg groups compared to the placebo group ($P < 0.0001$ for both RBP-6000 groups; Figure 12).

Figure 12: Kaplan-Meier Analysis of Retention in the Ph3DB Study (FAS)



5.1.3 *Subject Demographic and Baseline Characteristics*

Table 6 provides a summary of demographic and baseline characteristics. The mean age of subjects across all groups was approximately 40 years old (range 19 to 64 years). Approximately two-thirds of subjects in each group were male, and the study was well-represented with regard to black or African-American subjects, as well as those of Hispanic or Latino ethnicity. Baseline BMI was similar across treatment groups.

Table 6: Demographic and Baseline Characteristics in the Ph3DB Study (FAS)

Subject Characteristics	RBP-6000 300/300 mg (N=196)	RBP-6000 300/100 mg (N=194)	Placebo (N=99)
Age (years)			
Mean (SD)	39 (11)	40 (11)	39 (11)
Median (Min, Max)	38 (19, 64)	39 (20, 64)	38 (20, 63)
Age (years) by categories, n (%)			
≥18 to <30	43 (22%)	39 (20%)	23 (23%)
≥30 to <45	93 (47%)	84 (43%)	44 (44%)
≥45 to <60	52 (27%)	64 (33%)	30 (30%)
≥60	8 (4%)	7 (4%)	2 (2%)
Sex, n (%)			
Male	132 (67%)	128 (66%)	64 (65%)
Female	64 (33%)	66 (34%)	35 (35%)
Race, n (%)			
White	140 (71%)	132 (68%)	77 (78%)
Black or African American	54 (28%)	56 (29%)	20 (20%)
American Indian or Alaska Native	1 (< 1%)	4 (2%)	1 (1%)
Multiple	1 (< 1%)	2 (1%)	1 (1%)
Hispanic or Latino Ethnicity, n (%)	18 (9%)	12 (6%)	10 (10%)
Baseline BMI (kg/m^2)			
Mean (SD)	26 (4)	25 (4)	25 (4)
Median (Min, Max)	26 (18, 35)	25 (18, 35)	25 (18, 35)
Alcohol Use, n (%)	155 (79%)	152 (78%)	80 (81%)
Tobacco Use, n (%)	181 (92%)	178 (92%)	92 (93%)

Across the treatment groups, approximately one-third of subjects had a diagnosis of moderate OUD and approximately two-thirds had a diagnosis of severe OUD per DSM-5 criteria. Opioid use was long-standing in most subjects, with more than half of subjects reporting a history of opioid use of at least 8 years. With regard to route of administration, 41%-51% of subjects reported opioid use by the injectable route and 58%-71% reported opioid use by a non-injectable route at baseline. The most frequently reported illicit substances were opioids, cannabinoids, cocaine, and amphetamines/methamphetamine (Table 7).

Table 7: Drug Use History in the Ph3DB Study (FAS)

Characteristic	RBP-6000 300/300 mg (N=196)	RBP-6000 300/100 mg (N=194)	Placebo (N=99)
Severity of OUD, n (%)			
Moderate	67 (34%)	49 (26%)	31 (32%)
Severe	128 (66%)	142 (74%)	67 (68%)
Lifetime Opioid Use (years), n (%)			
< 4	41 (21%)	37 (19%)	17 (17%)
≥ 4 to < 8	46 (24%)	51 (27%)	20 (20%)
≥ 8 to < 15	47 (24%)	39 (20%)	32 (33%)
≥ 15	61 (31%)	64 (34%)	29 (30%)
Lifetime Opioid Use (years), mean (SD)	11 (9)	12 (10)	11 (9)
Users of Opioids by Injectable Route[a], n (%)			
Injecting Users	80 (41%)	84 (43%)	50 (51%)
Non-injecting Users	115 (59%)	110 (57%)	49 (49%)
Use of Other Substance, n (%)			
Cannabinoids	93 (47%)	106 (55%)	52 (53%)
Cocaine	78 (40%)	92 (47%)	42 (42%)
Amphetamines/Methamphetamine	29 (15%)	49 (25%)	19 (19%)
Methadone	14 (7%)	25 (13%)	5 (5%)
Benzodiazepines	20 (10%)	24 (12%)	13 (13%)
Buprenorphine	16 (8%)	20 (10%)	6 (6%)
Barbiturates	1 (< 1%)	3 (2%)	0
Phencyclidine	2 (1%)	0	1 (1%)
Other	5 (3%)	0	1 (1%)

[a] Injecting users reflect subjects who used by injectable route alone *or* both injectable and non-injectable routes. Non-injecting users reflect subjects who reported using only by the non-injectable route.

5.1.4 *Primary Endpoint – Percentage Abstinence*

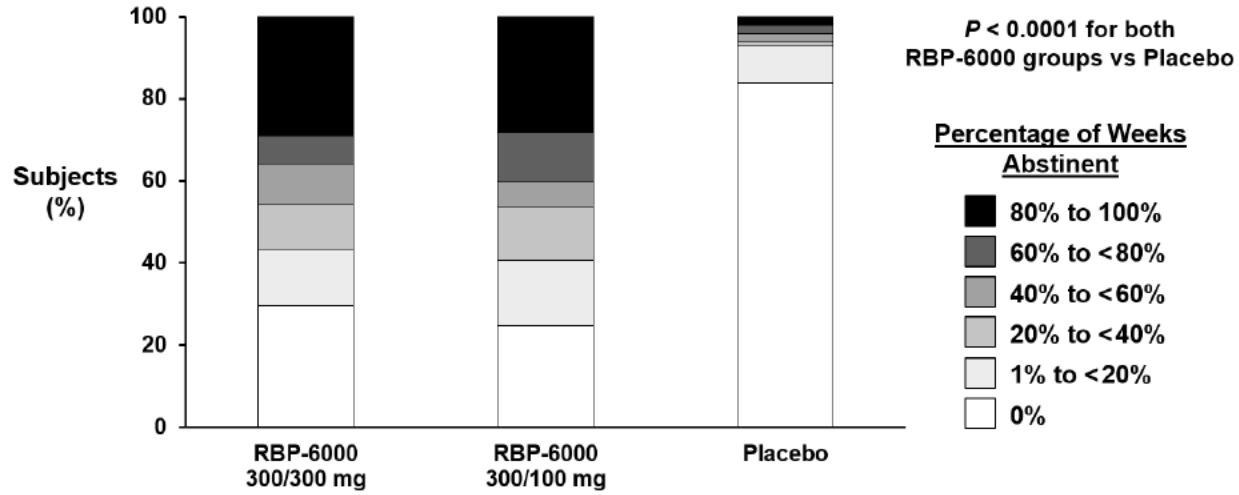
The efficacy of RBP-6000 was demonstrated for both the 300/300-mg and 300/100-mg dose groups. The primary efficacy endpoint, the percentage abstinence (i.e., proportion of opioid-free weeks) from Week 5 through Week 24, was statistically significantly greater in both the RBP-6000 groups compared with the placebo group ($P < 0.0001$ for both RBP-6000 groups vs placebo). The mean (median) percentage abstinence was 41% (30%), 43% (33%), and 5% (0%) for the 300/300-mg, 300/100-mg, and placebo groups, respectively (Table 8 and Figure 13).

Table 8: Summary Statistics for Percentage Abstinence from Week 5 through Week 24 (UDS + Self-report) in the Ph3DB Study (FAS)

Group	Mean (SD)	Median (IQR)	Percent of Subjects			
			0%	≥ 50%	≥ 80%	100%
300/300 mg	41% (40%)	30% (0% - 85%)	30%	42%	29%	12%
300/100 mg	43% (38%)	33% (5% - 80%)	25%	44%	28%	13%
Placebo	5% (17%)	0% (0% - 0%)	84%	4%	2%	1%

SD = standard deviation. IQR = interquartile range (25th and 75th percentiles).

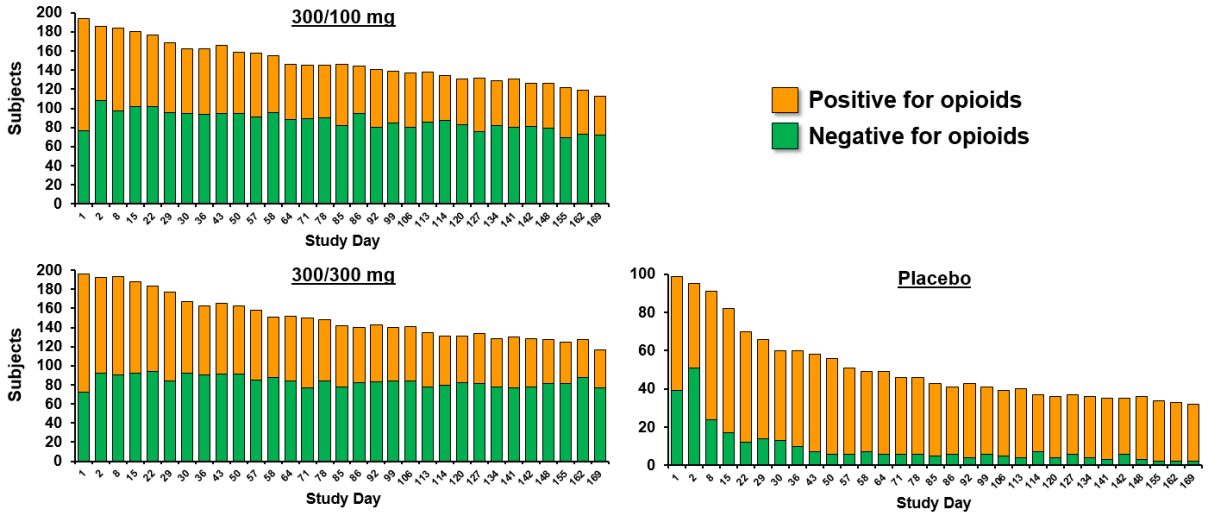
Figure 13: Primary Efficacy Endpoint: Percentage Abstinence from Week 5 through Week 24 (UDS + Self-report) in the Ph3DB Study (FAS)



5.1.4.1 *Additional Analyses of Percentage Abstinence (UDS + Self-report)*

Sensitivity analyses were also performed to evaluate the observed data without imputation for missing data. Figure 14 displays the number of subjects at each study visit that were positive and negative for illicit opioid use (note: missing data due to discontinuation or a missed study visit are not plotted, so the number of subjects in the plots tend to decrease over time). For both the 300/300-mg and 300/100-mg groups, the number of subjects who were negative for opioid use remained relatively consistent throughout follow-up. In the placebo group, the number of subjects who were negative for opioids declined rapidly following randomization to placebo and remained low throughout the treatment period.

Figure 14: Number of Subjects Negative and Positive for Illicit Opioid Use (UDS + Self-report) by Visit without Imputation for Missing Data (FAS)



Note: Study Day 1 is the end of the SUBOXONE run-in period. Study Day 2 reflects 24 hours after the first SC injection of RBP-6000 or placebo.

Figure 15 provides a summary of percentage abstinence in each group during the treatment period without imputation for missing data. The results from this sensitivity analysis support the findings from the primary analysis of the primary efficacy endpoint, which imputed all missing data as positive for opioids.

Figure 15: Percentage Abstinence from Week 5 through Week 24 (UDS + Self-report) in the Ph3DB Study without Imputation for Missing Data (FAS)

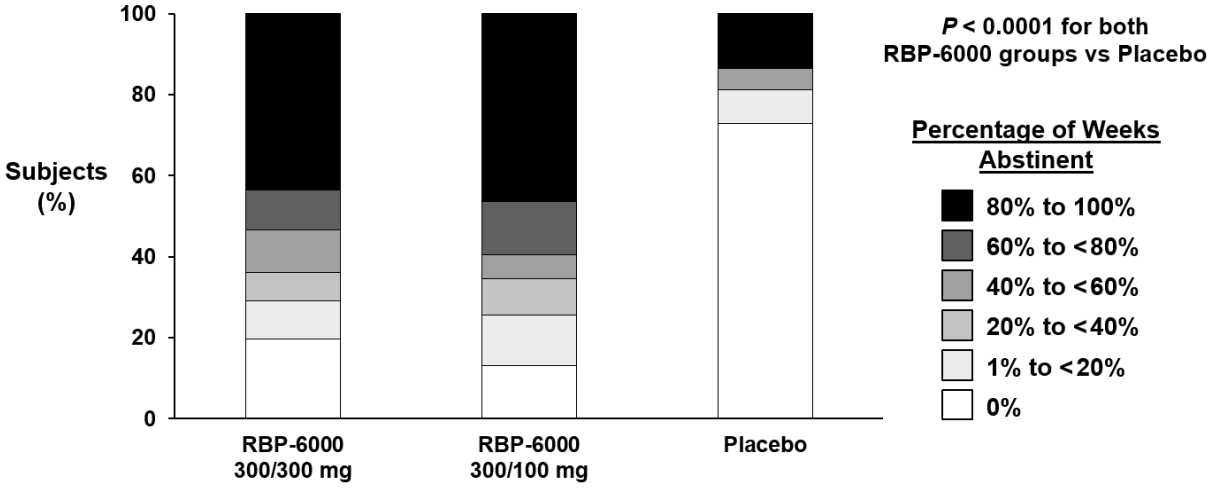
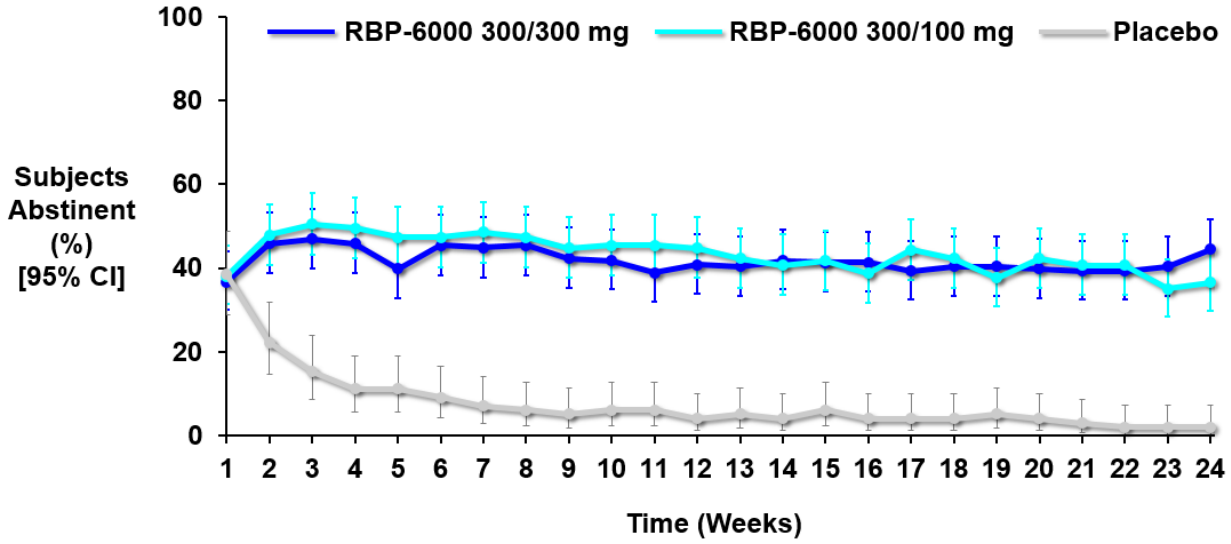


Figure 16 shows the time course of abstinence by group over the entire double-blind treatment period (including the "grace period"). Consistent with the primary efficacy endpoint analysis, missing data due to missed visits or treatment discontinuation were treated as positive for opioids. A substantial proportion of subjects in the RBP-6000 groups achieved abstinence early

in the study, and the percent of subjects who were abstinent by visit remained consistent throughout the 24-week study. In contrast, few subjects in the placebo group were abstinent after starting the study. This figure also illustrates that the "grace period" had minimal impact on the overall efficacy conclusions.

Figure 16: Percentage of Subjects Abstinent (by UDS + Self-report) by Week in the Ph3DB Study (FAS)



5.1.4.2 *Abstinence at Week 24 and Total Weeks Abstinent*

The percentage of subjects in the FAS who were abstinent (UDS + self-report) at Week 24 was statistically significantly higher in both the 300/300-mg (44%) and 300/100-mg (37%) groups than the placebo group (2%), respectively ($P < 0.0001$ for both RBP-6000 groups vs placebo).

From Week 5 through Week 24 in the FAS, the average number of weeks abstinent was statistically significantly higher for both the 300/300-mg and 300/100-mg groups (8.5 weeks for both groups) compared to the placebo group (1 week; $P < 0.0001$ for both RBP-6000 groups vs placebo).

5.1.4.3 *Subgroup Analyses of Percentage Abstinence*

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. Among subjects who used opioids by an injectable route, the mean [median] percentage abstinence was higher in the 300/300-mg group (45% [40%]) than in the 300/100-mg group (36% [20%]); and, among subjects who used opioids by a non-injectable route, the mean [median] percentage abstinence was higher in the 300/100-mg group (48% [48%]) than in the 300/300-mg group (39% [25%]) (Table 9).

Additional exploratory analyses were conducted among subjects completing the study to evaluate this difference by assessing the rate of continuous abstinence stratified by injecting vs. non-injecting users from Weeks 21-24, which was when differences in buprenorphine plasma

concentrations between the 300/300-mg and 300/100-mg groups were the greatest. Among injectable users, the percentage of subjects with continuous abstinence from Weeks 21-24 was 34% (27/80) in the 300/300-mg group and 18% (15/84) in the 300/100-mg group. There was no relevant difference in continuous abstinence from Weeks 21-24 between the dosing regimens among non-injecting users; the percentage of subjects with continuous abstinence was 28% in both RBP-6000 groups (300/300 mg: 32/115; 300/100 mg: 31/110). This finding among injecting opioid users in the study is consistent with prior research which suggests that higher buprenorphine exposures can be required in individuals who use high doses of opioids (Greenwald et al. 2014).

Table 9: Percentage Abstinence from Week 5 through Week 24 by Subgroup (FAS)

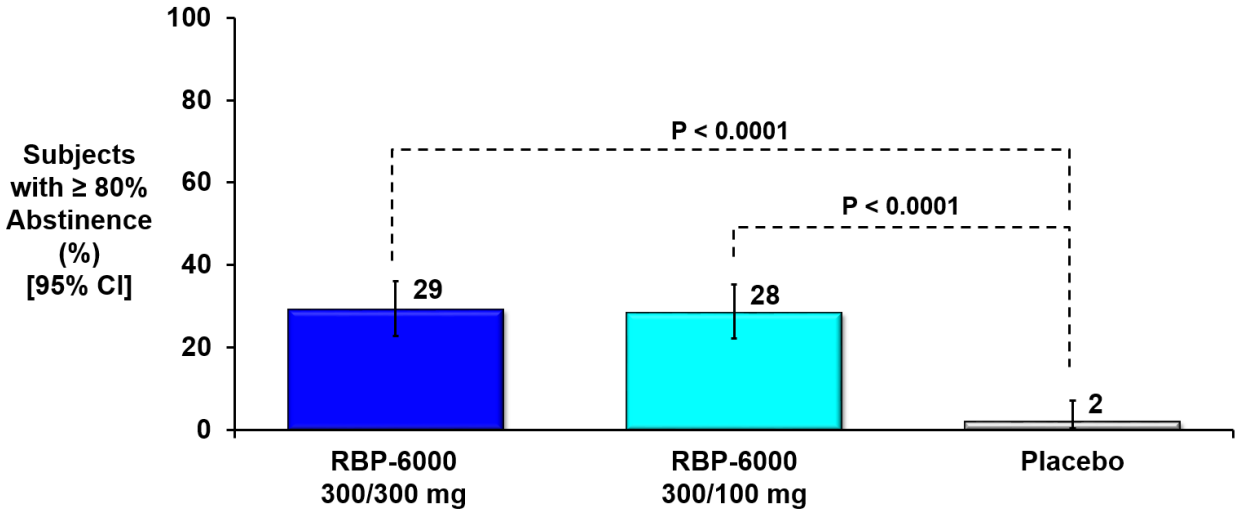
	RBP-6000 300/300-mg		RBP-6000 300/100-mg		Placebo	
	n	Mean (Median)	N	Mean (Median)	n	Mean (Median)
Sex						
Male	132	42% (35%)	128	41% (25%)	64	5% (0%)
Female	64	41% (25%)	66	46% (43%)	35	5% (0%)
Age, years						
≥ 18 and < 30	43	50% (50%)	39	43% (40%)	23	4% (0%)
≥ 30 and < 45	93	39% (30%)	84	40% (25%)	44	8% (0%)
≥ 45 and < 60	52	41% (30%)	64	47% (40%)	30	1% (0%)
≥ 60	8	24% (10%)	7	33% (10%)	2	0% (0%)
Race						
White	140	45% (38%)	132	45% (40%)	77	5% (0%)
Non-White	56	32% (10%)	62	38% (23%)	22	6% (0%)
BMI, kg/m^2						
> 0 to < 18.5	2	38% (38%)	6	32% (28%)	3	0% (0%)
≥ 18.5 to < 25	87	41% (35%)	94	41% (25%)	46	9% (0%)
≥ 25 to < 30	54	43% (33%)	64	35% (23%)	31	2% (0%)
≥30	53	40% (30%)	30	67% (78%)	19	2% (0%))
Users of Opioids by Injectable Route[a]						
Injecting Users	80	45% (40%)	84	36% (20%)	50	7% (0%)
Non-injecting Users	115	39% (25%)	110	48% (48%)	49	3% (0%)
Geographic Region						
Midwest	47	44% (40%)	42	36% (15%)	17	7% (0%)
Northeast	49	49% (50%)	46	57% (68%)	26	2% (0%)
South	82	38% (25%)	84	43% (33%)	47	5% (0%)
West	18	31% (0%)	22	27% (15%)	9	10% (0%)
Severity						
Moderate	67	41% (35%)	49	41% (35%)	31	4% (0%)
Severe	128	42% (30%)	142	44% (35%)	67	6% (0%)
Lifetime Opioid Use, years						
> 0 to < 4	41	39% (15%)	37	37% (20%)	17	6% (0%)
≥ 4 to < 8	46	48% (50%)	51	43% (35%)	20	0% (0%)
≥ 8 to < 15	47	44% (35%)	39	48% (40%)	32	5% (0%)
≥ 15	61	36% (25%)	64	45% (35%)	29	8% (0%)

[a] Injecting users reflect subjects who used by injectable route alone or both injectable and non-injectable routes. Non-injecting users reflect subjects who reported using only by the non-injectable route.

5.1.5 *Key Secondary Endpoint*

The key secondary endpoint of treatment success (≥ 80% abstinence from Week 5 through Week 24) was statistically significantly higher in the 300/300-mg and 300/100-mg groups compared with the placebo group: 29.1% and 28.4% versus 2.0%, respectively ($P < 0.0001$ for both RBP-6000 groups compared to the placebo group [Figure 17]).

Figure 17: Key Secondary Efficacy Endpoint: Percentage of Subjects Meeting Criterion for Treatment Success (≥ 80% Negative UDS + Self-report) in the Ph3DB Study (FAS)



5.1.6 *Other Secondary Endpoints*

An overview of the secondary efficacy endpoint results is shown in Table 10. None of these measures have validated minimal clinically important differences (MCID) for the OUD patient population.

Table 10: Secondary Endpoint Analysis by Mixed Model for Repeated Measures for Change from Baseline to Week 24 in the Ph3DB Study (FAS)

Change from Baseline to Week 24 RBP-6000 or Placebo	LS Mean (SE) Change from Baseline to Week 24	95% CI	*P*-value
Opioid Craving Visual Analog Scale Scores (VAS)			
RBP-6000 300/300 mg	-0.9 (1.6)	-4.1, 2.3	0.59
RBP-6000 300/100 mg	2.1 (1.6)	-1.2, 5.3	0.21
Placebo	11.5 (2.5)	6.6, 16.4	< 0.0001
Clinical Opiate Withdrawal Scale (COWS)			
RBP-6000 300/300 mg	-1.1 (0.2)	-1.5, -0.7	< 0.0001
RBP-6000 300/100 mg	-0.5 (0.2)	-0.9, -0.1	0.018
Placebo	-0.1 (0.4)	-0.8, 0.6	0.70
Subjective Opiate Withdrawal Scale (SOWS)			
RBP-6000 300/300 mg	-2.0 (0.5)	-3.0, -0.9	0.0002
RBP-6000 300/100 mg	-0.9 (0.5)	-1.9, 0.1	0.076
Placebo	0.7 (0.8)	-0.9, 2.2	0.41
Pairwise Comparisons:	**Difference in LS means (SE)**	**95% CI**	***P*-value**
Opioid Craving Visual Analog Scale Scores (VAS)			
RBP-6000 300/300 mg vs. placebo	-12.4 (2.6)	-17.5, -7.3	< 0.0001
RBP-6000 300/100 mg vs. placebo	-9.4 (2.6)	-14.6, -4.3	0.0003
Clinical Opiate Withdrawal Scale (COWS)			
RBP-6000 300/300 mg vs. placebo	-1.0 (0.4)	-1.7, -0.2	0.010
RBP-6000 300/100 mg vs. placebo	-0.4 (0.4)	-1.1, 0.4	0.31
Subjective Opiate Withdrawal Scale (SOWS)			
RBP-6000 300/300 mg vs. placebo	-2.6 (0.9)	-4.3, -0.9	0.003
RBP-6000 300/100 mg vs. placebo	-1.6 (0.9)	-3.3, 0.1	0.073

5.1.6.1 *Opioid Craving VAS*

The RBP-6000 groups had significantly greater decreases in Opioid Craving VAS from baseline to Week 24 than the placebo group. (For reference, the Opioid Craving VAS is measured on a 0 to 100 mm scale where 0 corresponds to "no craving" and 100 corresponds to "strongest craving ever".) Figure 18 illustrates the estimated mean Opioid Craving VAS scores by group over time based on MMRM analysis. The difference in least squares (LS) means for the change from baseline to Week 24 compared to placebo was statistically significant for the 300/300-mg group (-12.4; $P < 0.0001$) and the 300/100-mg group (-9.4; $P = 0.0003$).

Figure 18: Estimated Mean Opioid Craving VAS Scores from Week 1 through Week 24 in the Ph3DB Study Based on MMRM (FAS)

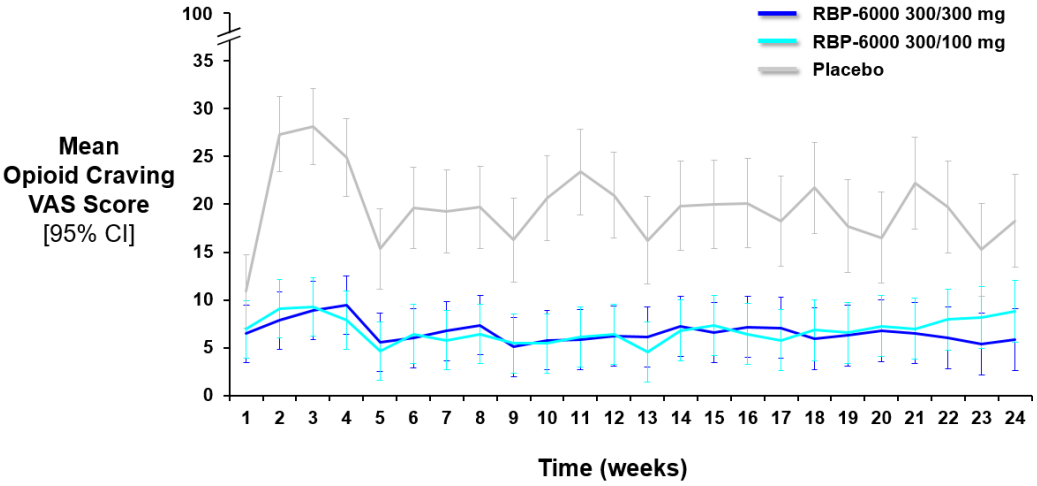
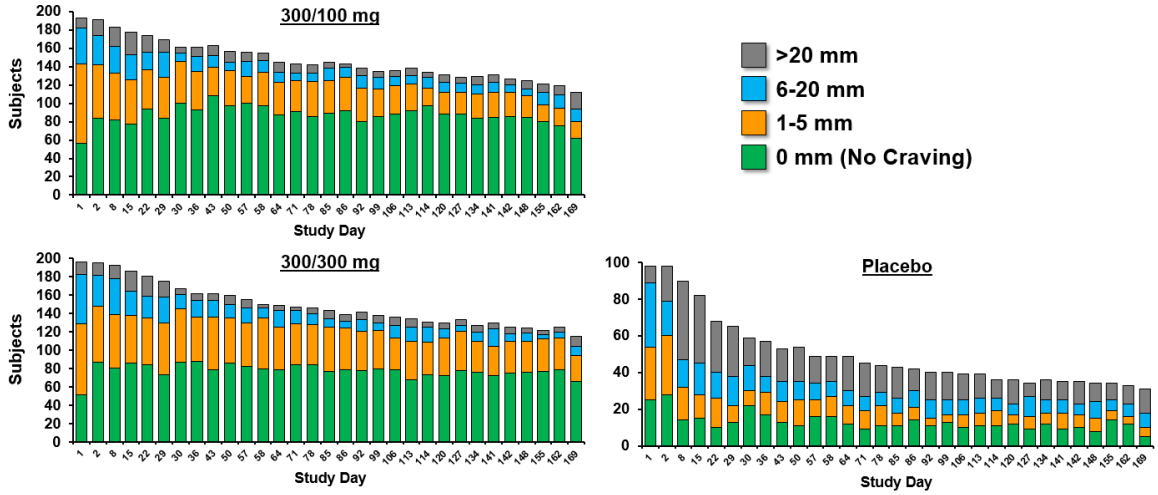


Figure 19 provides a summary of results for the Opioid Craving VAS using various thresholds for response without imputation. Importantly a much larger number of subjects in the RBP-6000 treatment groups reported low (≤ 5 mm) or no (0 mm) craving compared to the placebo subjects.

Figure 19: Number of Subjects with Opioid Craving VAS Scores of 0, 1-5, 6-20, or >20 mm by Visit (FAS)



Note: Study Day 1 is the end of the SUBOXONE run-in period. Study Day 2 reflects 24 hours after the first SC injection of RBP-6000 or placebo.

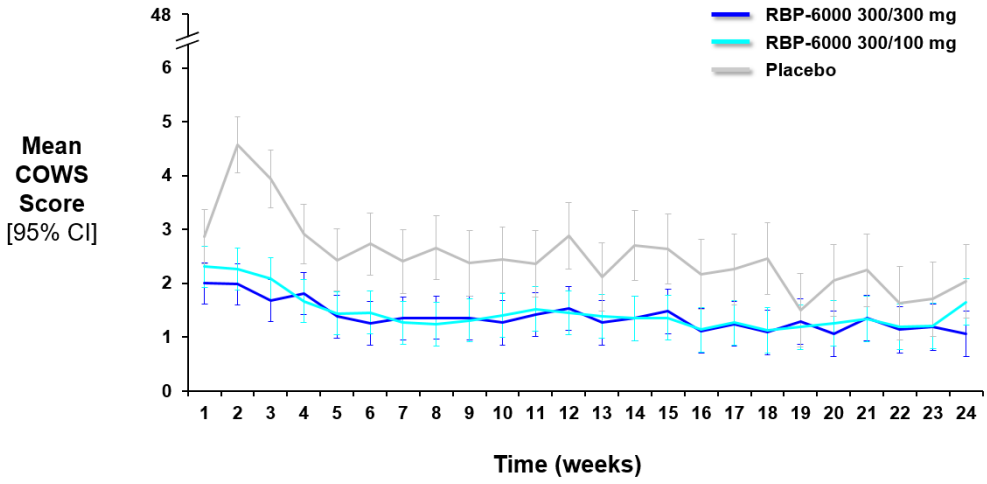
An additional analysis used MMRM models to estimate time-averaged responder estimates for the percentage of subjects who had control of opioid craving during the study (defined as a score ≤ 5 mm on the 0-100 mm scale from Weeks 1 to 24). The estimated percentage of subjects with control of craving was 81% (95% CI: 77-84), 81% (95% CI: 77-84), and 48% (95% CI: 41-56) in the 300/300-mg, 300/100-mg, and placebo groups, respectively. The relatively high rate of response for control of craving in the placebo group is impacted by the higher use of illicit opioids during the treatment period.

5.1.6.2 *COWS*

Figure 20 illustrates the estimated mean COWS scores by group over time based on MMRM analysis. (For reference, scores 5-12 are considered mild symptoms, scores 13-24 are considered moderate symptoms, scores 25-36 are considered moderately severe, and scores higher than 36 are considered severe withdrawal.)

The difference in LS mean change from baseline in COWS scores for the RBP-6000 groups at Week 24 compared with placebo was statistically significant for the 300/300-mg group (-1.0, $P = 0.01$), but was not for the 300/100-mg group (-0.4, $P = 0.31$). Neither treatment differences between RBP-6000 groups and placebo can be considered clinically meaningful differences; however, interpretation of these scores should acknowledge that these treatment differences reflect change from baseline where subjects' opioid craving and withdrawal symptoms were already controlled on SUBOXONE and that withdrawal scores for the placebo group are impacted by the higher use of illicit opioids during the treatment period.

Figure 20: Estimated Mean Clinical Opiate Withdrawal Scale (COWS) Scores from Week 1 through Week 24 in the Ph3DB Study Based on MMRM (FAS)



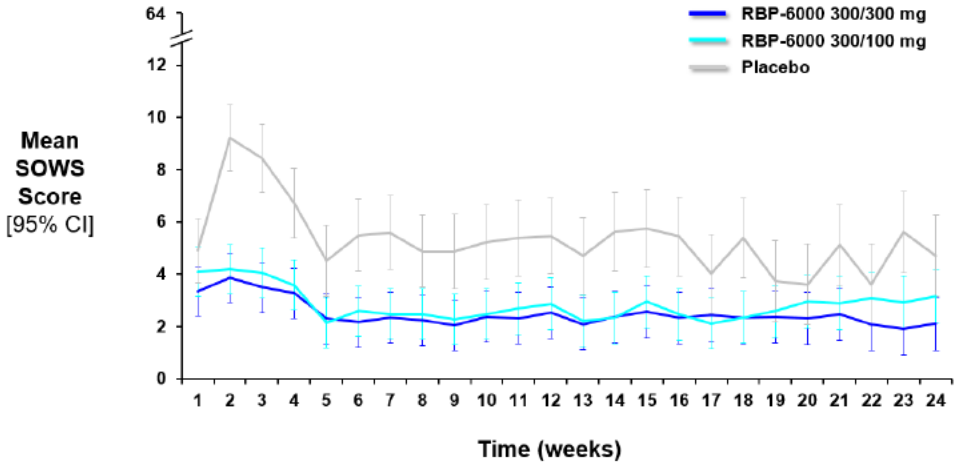
An additional analysis used MMRM models to estimate the percentage of subjects with control of withdrawal symptoms during the treatment period (defined as COWS scores ≤ 12 from Weeks 1-24). The estimated percentage of subjects with control of withdrawal symptoms was high in all groups: 99.7% (95% CI: 99.1-99.9), 99.6% (95% CI: 99.1-99.8), and 97% (95% CI: 96-98) for the 300/300-mg, 300/100-mg, and placebo groups, respectively.

5.1.6.3 *SOWS*

The mean total scores for the SOWS were low, indicating a lack of clinically important opioid withdrawal symptomatology. (For reference, the SOWS is scored based on 16 symptoms of withdrawal rated in intensity on a 5-point ordinal scale. The total score is a sum of the item ratings and ranges from 0 to 64.) Figure 21 illustrates the estimated mean SOWS scores by group over time based on MMRM analysis. The difference in LS mean change from baseline for the RBP-6000 groups at Week 24 compared with placebo was statistically significant for the

300/300-mg group (-2.6, $P = 0.003$), but not for the 300/100-mg group (-1.6; $P = 0.07$). Neither treatment difference can be considered clinically meaningful.

Figure 21: Estimated Mean Subjective Opiate Withdrawal Scale (SOWS) Scores from Baseline through Week 24 in the Ph3DB Study Based on MMRM (FAS)



5.1.6.4 *Percentage Abstinence Based on UDS Only*

In the FAS, the mean percentage abstinence for opioids based on UDS only was statistically significantly higher in both the 300/300-mg (44%) and 300/100-mg (46%) groups compared with the placebo group (7%), respectively ($P < 0.0001$ for both RBP-6000 treatment groups compared to placebo; Table 11). These results based on UDS only are consistent with the primary endpoint definition, which is based on UDS + self-report.

Table 11: Percentage of Urine Samples Negative for Opioids from Week 5 through Week 24 in the Ph3DB Study (FAS)

% Urine Samples Negative for Opioids	RBP-6000 300/300 mg (N = 196)	RBP-6000 300/100 mg (N = 194)	Placebo (N = 99)
≥ 0%	196 (100%)	194 (100%)	99 (100%)
≥ 10%	129 (66%)	140 (72%)	17 (17%)
≥ 20%	114 (58%)	120 (62%)	9 (9%)
≥ 30%	109 (56%)	106 (55%)	8 (8%)
≥ 40%	98 (50%)	97 (50%)	7 (7%)
≥ 50%	88 (45%)	91 (47%)	6 (6%)
≥ 60%	74 (38%)	82 (42%)	5 (5%)
≥ 70%	69 (35%)	73 (38%)	4 (4%)
≥ 80%	61 (31%)	64 (33%)	4 (4%)
≥ 90%	51 (26%)	47 (24%)	2 (2%)
P-value (comparison with Placebo)	< 0.0001	< 0.0001	
Mean (SD)	44% (40%)	46% (40%)	7% (19%)
Median	38%	38%	0%

5.1.6.5 *Percentage Abstinence Based on Self-Reports Only*

In the FAS, the mean percentage abstinence from opioids based on self-report (TLFB interview) only was statistically significantly higher in both the 300/300-mg (62%) and 300/100-mg (63%) groups compared with the placebo group (19%), respectively ($P < 0.0001$ for both RBP-6000 groups compared to placebo; Table 12).

Table 12: Percentage of Self-Reports Negative for Illicit Opioid Use from Week 5 Through Week 24 in the Ph3DB Study (FAS)

% Self-Reports Negative for Illicit Opioid Use	RBP-6000 300/300 mg (N = 196)	RBP-6000 300/100 mg (N = 194)	Placebo (N = 99)
≥ 0%	196 (100%)	194 (100%)	99 (100%)
≥ 10%	162 (83%)	163 (84%)	37 (37%)
≥ 20%	152 (78%)	155 (80%)	29 (29%)
≥ 30%	139 (71%)	139 (72%)	24 (24%)
≥ 40%	132 (67%)	132 (68%)	20 (20%)
≥ 50%	125 (64%)	125 (64%)	18 (18%)
≥ 60%	117 (60%)	120 (62%)	17 (17%)
≥ 70%	112 (57%)	108 (56%)	14 (14%)
≥ 80%	101 (52%)	102 (53%)	9 (9%)
≥ 90%	91 (46%)	92 (47%)	7 (7%)
P-value (comparison with Placebo)	< 0.0001	< 0.0001	
Mean (SD)	62% (40%)	63% (39%)	19% (31%)
Median	85%	85%	0%

5.1.7 ***Employment Status***

Self-reports of employment status were collected at regular intervals throughout the Ph3DB study to evaluate the impact of treatment on clinically important indicators of social and economic stability. Complete-case analyses were performed on subjects with measurements at both baseline and Week 24 using logistic regression models with the Week 24 status (unemployed) as the outcome variable and predictor variables of baseline employment status and treatment group.

The percentages of subjects who were employed increased in the RBP-6000 groups and decreased in the placebo group (Table 13). Among subjects who had both baseline and Week 24 values, the percentage of subjects who were employed increased by 15 percentage points in the 300/300-mg group ($P = 0.011$ vs. placebo), increased by 10 percentage points in the 300/100-mg group ($P = 0.093$ vs. placebo), and decreased by 5 percentage points in the placebo group.

Table 13: Employment Status at Baseline and End of Study in the Ph3DB Study

	RBP-6000 300/300 mg (N = 195)	RBP-6000 300/100 mg (N = 193)	Placebo (N = 98)
Employed at Baseline, n/N (%)	46/130 (35%)	43/125 (34%)	15/38 (39%)
Employed at End of Study, n/N (%)	66/130 (51%)	55/125 (44%)	13/38 (34%)
Difference in Employment Status	+15%	+10%	-5%
P-value vs. Placebo	0.011	0.093	

5.1.8 *Exposure-Response Analyses*

Exposure-response relationships for abstinence (UDS + self-report), opioid craving, COWS scores and SOWS scores were assessed in the Ph3DB study using observed data without imputation. For these analyses, each buprenorphine plasma concentration in the study, beginning with Study Day 1 (end of the run-in period), was categorized into different ranges. The probability of abstinence or a particular responder threshold for the Opioid Craving VAS or COWS was calculated for each of the buprenorphine concentration categories to provide an exposure-response curve.

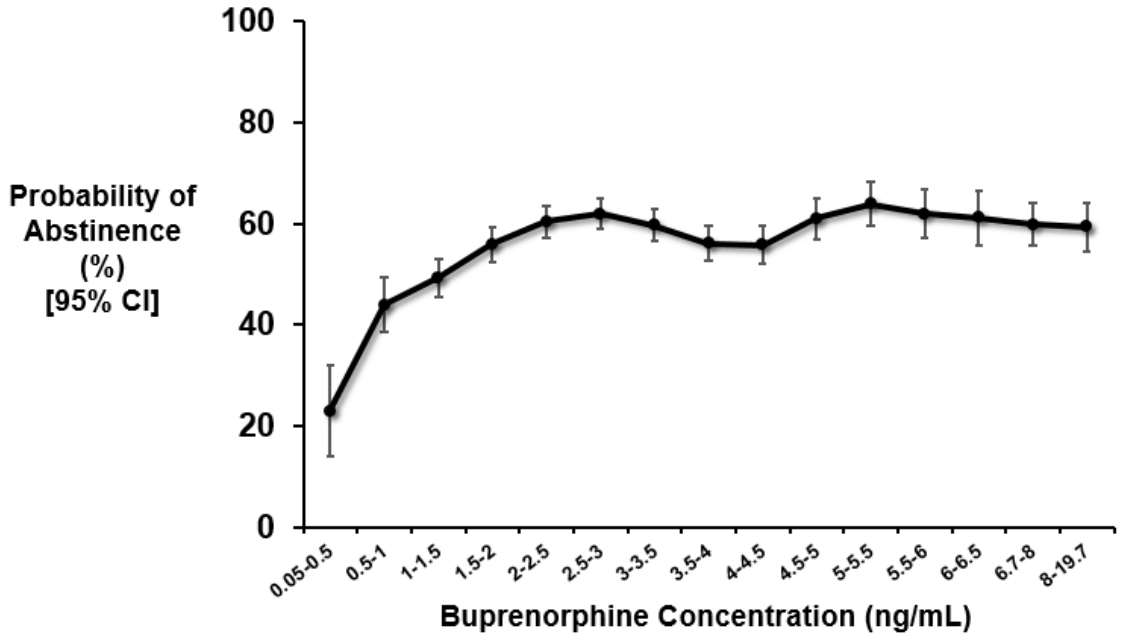
Table 14 provides estimated mean PK parameters after 6 injections of RBP-6000 in the 300/100-mg and 300/300-mg groups to provide a basis for evaluating the exposure-response analyses.

Table 14: Estimated Mean Buprenorphine 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

RBP-6000 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

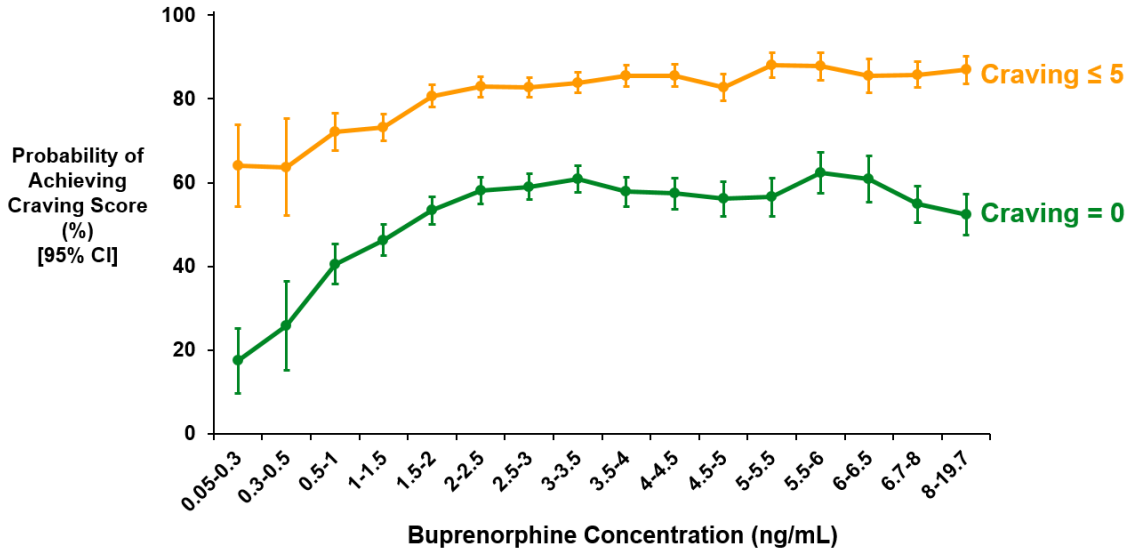
For abstinence, the observed plateau for maximal response was reached at approximately 2-3 ng/mL (Figure 22). This finding is consistent with previous analyses identifying 2-3 ng/mL as plasma concentrations associated with opioid blockade (Greenwald et al. 2014; Nasser et al. 2014).

Figure 22: Exposure-Response Analysis for Abstinence



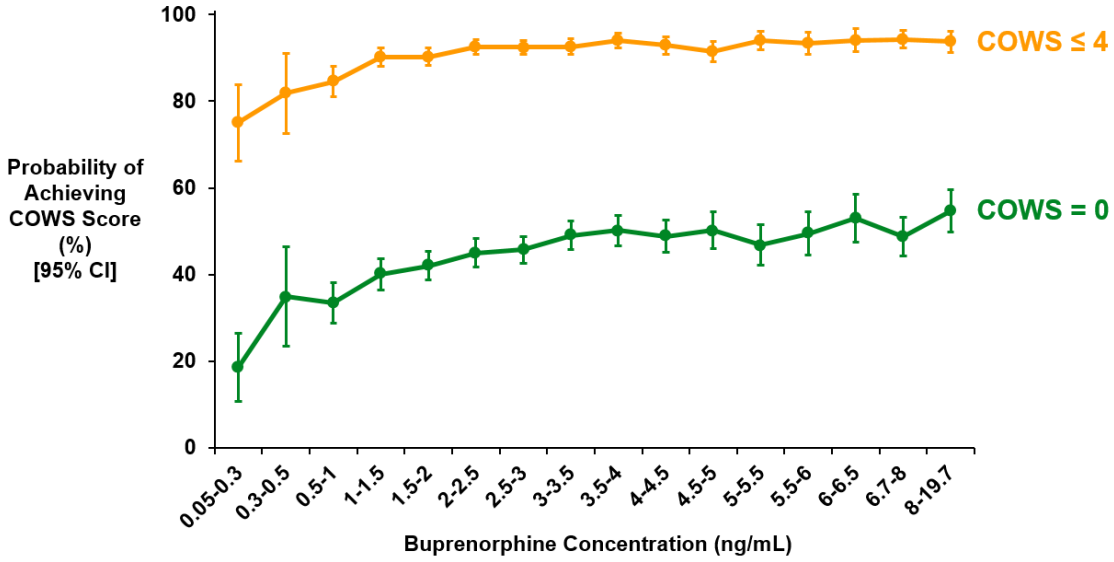
The observed plateau for maximal response on the 100-point Opioid Craving VAS for a craving score ≤ 5 and for craving score of 0 (i.e., "no craving") was reached at approximately 3-3.5 ng/mL (Figure 23).

Figure 23: Exposure-Response Analysis for Opioid Craving VAS



Withdrawal signs and symptoms (COWS) were clinically controlled (defined as ≤ 12 on a 48-point scale) in nearly all subjects. However, the observed maximal response to achieve a COWS score of 0 (i.e., no signs or symptoms of withdrawal) was reached at approximately 3.5-4 ng/mL.

Figure 24: Exposure-Response Analysis for COWS



5.2 Phase 3 Open-Label Study 13-0003

5.2.1 *Study Design*

The Ph3OL study is a recently concluded Phase 3, open-label, multicenter, long-term safety and tolerability study of RBP-6000 in treatment-seeking subjects with moderate or severe OUD (DSM-5). The primary objective of the study was to evaluate long-term safety, however efficacy data were also collected.

The study included 2 groups: (1) the de-novo group, which included subjects who did not participate in the Ph3DB study and (2) the roll-over group, which included subjects who completed the Ph3DB study. Subjects in the de-novo group had a 48-week treatment phase with up to 12 injections of RBP-6000; subjects in the roll-over group had a 24-week treatment phase with up to 6 additional injections of RBP-6000. De-novo subjects were inducted onto SUBOXONE sublingual film prior to receiving RBP-6000. All subjects in the Ph3OL study received an initial 300-mg injection of RBP-6000. The choice of subsequent maintenance doses (300 mg or 100 mg) was at the discretion of the investigator (referred to as the RBP-6000 300/flex regimen hereafter).

To support the NDA, an interim analysis was performed for this study using data available as of the data cut-off date (12 August 2016). At that time, 669 subjects (412 de-novo subjects and 257 roll-over subjects) from 39 sites had entered the treatment period and received at least 1 dose of RBP-6000. There were 124 subjects at that time (2 de-novo subjects and 122 roll-over subjects)

who completed the study by receiving 6 injections (roll-over) or 12 injections (de-novo) of RBP-6000 and completing the end of study visit.

A total of 333 subjects overall were ongoing in the study (246 de-novo subjects and 87 roll-over subjects), and 212 subjects (31.7%) had discontinued during the treatment period (164 de-novo subjects and 48 roll-over subjects). The most common reasons for discontinuation from the treatment period were subject withdrawal of consent (76 subjects; 11.4%), lost to follow-up (72 subjects; 10.8%), and other (32 subjects; 4.8%). Few subjects (12 subjects; 1.8%) were withdrawn due to an AE; no subject died during the study.

Demographic and baseline characteristics were similar between de-novo and roll-over groups upon entry to the Ph3OL study (Table 15).

Table 15: Demographic and Baseline Characteristics in the Ph3OL Study

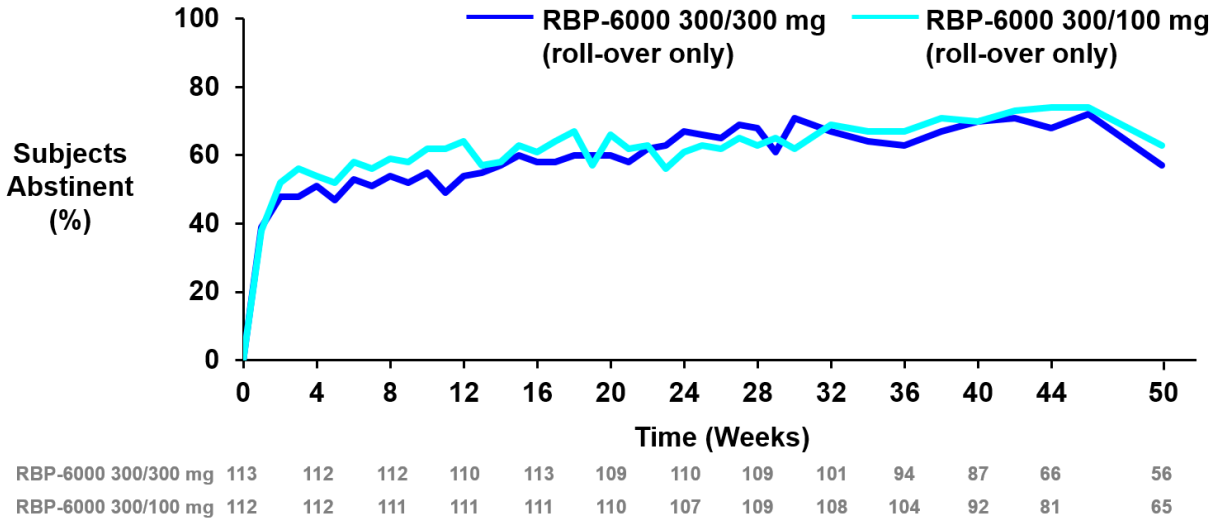
Subject Characteristics	RBP-6000 300/Flex		
	De-novo (N=412)	Roll-over (N=257)	Total (N=669)
Age (years)			
Mean (SD)	38 (12)	42 (11)	40 (12)
Median (Min, Max)	36 (19, 65)	40 (21, 64)	38 (19, 65)
Sex, n (%)			
Male	263 (64%)	169 (66%)	432 (65%)
Female	149 (36%)	88 (34%)	237 (35%)
Race, n (%)			
White	295 (72%)	168 (65%)	463 (69%)
Black or African American	107 (26%)	85 (33%)	192 (29%)
Native Hawaiian or Other Pacific Islander	0	1 (< 1%)	1 (< 1%)
American Indian or Alaska Native	2 (< 1%)	2 (< 1%)	4 (< 1%)
Asian	2 (< 1%)	0	2 (< 1%)
Multiple	2 (< 1%)	1 (< 1%)	3 (< 1%)
Other	4 (1%)	0	4 (< 1%)
Hispanic or Latino Ethnicity, n (%)	43 (10.4%)	16 (6%)	59 (9%)
Baseline BMI (kg/m^2)			
Mean (SD)	25 (4)	26 (5)	26 (5)
Median (Min, Max)	25 (18, 36)	25 (17, 42)	25 (17, 42)
Alcohol use, n (%)			
Never	122 (30%)	48 (19%)	170 (25%)
Former	97 (24%)	65 (25%)	162 (24%)
Current	193 (47%)	144 (56%)	337 (50%)
Tobacco use, n (%)			
Never	40 (10%)	23 (9%)	63 (9%)
Former	18 (4%)	12 (5%)	30 (4%)
Current	193 (47%)	222 (86%)	576 (86%)

5.2.2 *Maintenance of Efficacy*

The Ph3OL study was ongoing at the time of the data cut-off; however, preliminary data are included in this document to evaluate efficacy associated with up to 12 monthly injections of RBP-6000 utilizing data from the roll-over subjects, treating all missing results as positive for visits that were possible at the time of the analysis. Approximately 60% of subjects in both groups remained abstinent (UDS + self-report), providing support that the efficacy of RBP-6000

is sustained through 12 monthly injections (Figure 25). The smaller sample size toward the later weeks simply reflects that not all subjects had yet reached those weeks in the study, as this was an interim analysis.

Figure 25: Percentage of Subjects Abstinent by Subject Groups and Study Weeks for Roll-Over Subjects in the Ph3OL Study



For roll-over subjects, Week 1 to 24 data are from Study 13-0001. Week 25 onward for roll-over subjects corresponds to Week 1 onward in Study 13-0003 where subjects were on flex dosing.

5.3 Efficacy Conclusions

The pivotal Ph3DB study demonstrated the efficacy of both dosing regimens of RBP-6000, with persistent and statistically significant differences compared to placebo in percentage abstinence and treatment success. Treatment benefits were consistent across other important endpoints for individuals being treated for OUD, including reduction in craving and control of withdrawal symptoms. The benefits of RBP-6000 were evident after administration of the first dose and sustained for the entire treatment duration without the use of supplemental buprenorphine.

The overall efficacy profile of RBP-6000 was similar for the 300/300-mg and 300/100-mg dosing regimens across most of the important subgroups of clinical interest. Consistent with prior literature, injecting drug users achieved additional benefit from the higher buprenorphine dose. This finding, in the context of prior research, supports providing clinicians the option of selecting the 100-mg or 300-mg maintenance dose for each patient based on their clinical condition and an appreciation of the clinical factors known to impact the efficacy of buprenorphine.

Finally, data from the Ph3OL study provide further evidence of the durability of efficacy with RBP-6000 in the treatment of adults with OUD.

6 CLINICAL SAFETY

Summary

- The RBP-6000 safety database includes 1,083 individuals, 848 of whom were enrolled in the Phase 3 studies and received up to 12 monthly doses of RBP-6000.
- The safety profile of RBP-6000 is consistent with the known safety profile of other buprenorphine products indicated for the treatment of OUD, with the exception of anticipated injection site reactions, which were generally transient, mild or moderate in severity and were not treatment limiting.
- In Ph3DB study, injection site reaction TEAEs occurred in 18.9% and 13.8% of subjects in the 300/300-mg and 300/100-mg groups and in 9% of subjects in the placebo group. The higher rate of injection site reactions in the 300/300-mg group is consistent with the higher injection volume of the 300-mg dose.
- Elevated hepatic enzymes are consistent with the known safety profile of buprenorphine for OUD. The incidence of AST and ALT elevations in the 300/300-mg and 300/100-mg groups were similar to the rates reported in a hepatic safety study of SUBOXONE (24-week safety study with SUBOXONE that was conducted by NIDA. Elevated liver enzymes were reported more frequently in the 300/300-mg group than the 300/100-mg group.
- In the Ph3OL study, the frequently reported AEs in the de-novo group were similar to the rates observed in the active groups of the double-blind study. Furthermore, the incidence and types of AEs in the roll-over group did not increase as subjects continued treatment with RBP-6000.

6.1 Treatment Exposure

As of the data cut-off date of 12 August 2016, a total of 1,083 subjects received at least 1 injection of RBP-6000 across all studies, with 848 subjects in the Phase 3 studies and 235 in the Phase 1 and 2 studies

Data from the 2 Phase 3 studies provided:

- 557 subjects and 138 subjects with at least 6 injections and at least 12 injections, respectively.
- 532 subjects and 87 subjects with at least 24 weeks and at least 48 weeks of exposure, respectively.

For the RBP-6000 300-mg dose level, over the entire course of treatment:

- 452 subjects achieved at least 24 weeks of RBP-6000 exposure
- 37 subjects achieved at least 48 weeks of RBP-6000 exposure

All subjects in the Ph3OL study received an initial 300-mg injection of RBP-6000. Subsequent maintenance doses of 300 mg or 100 mg were determined at the discretion of the investigator (RBP-6000 300/flex regimen). Of the 669 subjects enrolled in the Ph3OL study, 468 (70%) remained on the 300-mg dose after the initial 300-mg injection.

See Appendix 10.2 for details on subject disposition in the Phase 3 studies.

6.2 Treatment-Emergent Adverse Events

In the Ph3DB study, any treatment-emergent adverse events (TEAEs) were reported in a higher percentage of subjects in the 300/300-mg and 300/100-mg groups compared with the placebo group as follows: 66.7% and 76.4% vs. 56.0%, respectively (Table 16). Serious TEAEs and TEAEs leading to discontinuation were similar across groups. There was 1 fatal SAE report (gunshot wound due to homicide) in the 300/300-mg group; this event was considered unrelated to RBP-6000 by the investigator.

The percentage of subjects in the 300/300-mg and 300/100-mg groups vs. the placebo group, respectively, with TEAEs by maximum severity, was as follows: mild (20.4% and 25.1% vs. 21.0%), moderate (39.8% and 43.8% vs. 31.0%) and severe (6.5% and 7.4% vs. 4.0%). No severe TEAE (by Preferred Term [PT]) was reported for > 1% of subjects in either RBP-6000 treatment group.

Table 16: Overall Summary of TEAEs in the Ph3DB Study

Number (%) of Subjects with Any:	RBP-6000 300/300 mg (N=201)	RBP-6000 300/100 mg (N=203)	Placebo (N=100)	RBP-6000 Total (N=404)
TEAE	134 (66.7%)	155 (76.4%)	56 (56.0%)	289 (71.5%)
Study Treatment-Related TEAE	70 (34.8%)	67 (33.0%)	23 (23.0%)	137 (33.9%)
Severe TEAE	13 (6.5%)	15 (7.4%)	4 (4.0%)	28 (6.9%)
Serious TEAE	7 (3.5%)	4 (2.0%)	5 (5.0%)	11 (2.7%)
Death	1 (0.5%)	0	0	1 (0.2%)
TEAE Leading to Study Treatment Discontinuation	10 (5.0%)	7 (3.4%)	2 (2.0%)	17 (4.2%)

Overall, the TEAE profile was consistent with the known safety profile for buprenorphine with the exception of anticipated injection site reactions. (Appendix 10.3 provides an overview of the safety of other buprenorphine products per the product label for SUBOXONE.) No individual TEAEs were reported in more than 10% of subjects in the RBP-6000 treatment groups; insomnia was reported in 11.0% of subjects in the placebo group. The most commonly reported (in ≥ 5% of subjects in the RBP-6000 groups) TEAEs in the combined active treatment groups (by PT) were headache, constipation, nausea, injection site pruritus, vomiting, insomnia, upper respiratory tract infection, injection site pain, nasopharyngitis, and fatigue. The percentage of subjects with the most commonly reported TEAEs was generally similar across treatment groups, although constipation was reported only in the active treatment groups and upper respiratory tract infection was reported more frequently in the active treatment groups compared with the placebo group.

Table 17: TEAEs Reported in at Least 5% of Subjects in Any Treatment Group During the Ph3DB Study

Preferred Term	RBP-6000 300/300 mg (N=201)	RBP-6000 300/100 mg (N=203)	Placebo (N=100)	RBP-6000 Total (N=404)
Any TEAE, n (%)	134 (66.7%)	155 (76.4%)	56 (56.0%)	289 (71.5%)
Headache	17 (8.5%)	19 (9.4%)	6 (6.0%)	36 (8.9%)
Constipation	16 (8.0%)	19 (9.4%)	0	35 (8.7%)
Nausea	16 (8.0%)	18 (8.9%)	5 (5.0%)	34 (8.4%)
Injection site pruritus	19 (9.5%)	13 (6.4%)	4 (4.0%)	32 (7.9%)
Vomiting	11 (5.5%)	19 (9.4%)	4 (4.0%)	30 (7.4%)
Insomnia	17 (8.5%)	13 (6.4%)	11 (11.0%)	30 (7.4%)
Upper respiratory tract infection	12 (6.0%)	15 (7.4%)	1 (1.0%)	27 (6.7%)
Injection site pain	12 (6.0%)	10 (4.9%)	3 (3.0%)	22 (5.4%)
Nasopharyngitis	10 (5.0%)	11 (5.4%)	1 (1.0%)	21 (5.2%)
Fatigue	12 (6.0%)	8 (3.9%)	3 (3.0%)	20 (5.0%)
Anxiety	8 (4.0%)	10 (4.9%)	5 (5.0%)	18 (4.5%)
Drug withdrawal syndrome	7 (3.5%)	9 (4.4%)	6 (6.0%)	16 (4.0%)
Blood creatinine phosphokinase increased	5 (2.5%)	11 (5.4%)	1 (1.0%)	16 (4.0%)
Diarrhoea	5 (2.5%)	5 (2.5%)	5 (5.0%)	10 (2.5%)

In the Ph3OL study, the percentage of subjects with TEAEs in the de-novo group was generally similar to those reported in the RBP-6000 total group in the Ph3DB study (Table 18).

Table 18: Overall Summary of TEAEs in the Treatment Phase of the Ph3OL Study

	RBP-6000 300/Flex		
Number (%) of Subjects with Any:	**De-novo (N=412)**	**Roll-over (N=257)**	**Total (N=669)**
TEAE	291 (70.6%)	141 (54.9%)	432 (64.6%)
Study Treatment-related TEAE	160 (38.8%)	60 (23.3%)	220 (32.9%)
Severe TEAE	35 (8.5%)	7 (2.7%)	42 (6.3%)
Serious TEAE	17 (4.1%)	9 (3.5%)	26 (3.9%)
Death	0	0	0
TEAE Leading to Study Treatment Discontinuation	11 (2.7%)	4 (1.6%)	15 (2.2%)

No individual TEAE was reported in ≥ 5% of subjects in the roll-over subject group. TEAEs reported in at least 5% of subjects in the de-novo subject group were constipation, nausea, injection site pain, insomnia, headache, nasopharyngitis, and injection site erythema (Table 19). The type and rate of TEAEs were similar to those reported in the Ph3DB study.

Table 19: TEAEs Reported in ≥ 5% of Subjects in Any Subject Group in the Treatment Phase of the Ph3OL Study

Preferred Term	RBP-6000 300/Flex		
	De-novo (N=412)	Roll-over (N=257)	Total (N=669)
Any TEAE, n (%)	291 (70.6%)	141 (54.9%)	432 (64.6%)
Constipation	48 (11.7%)	9 (3.5%)	57 (8.5%)
Nausea	34 (8.3%)	11 (4.3%)	45 (6.7%)
Injection site pain	33 (8.0%)	8 (3.1%)	41 (6.1%)
Insomnia	26 (6.3%)	11 (4.3%)	37 (5.5%)
Headache	30 (7.3%)	3 (1.2%)	33 (4.9%)
Nasopharyngitis	24 (5.8%)	4 (1.6%)	28 (4.2%)
Injection site erythema	21 (5.1%)	5 (1.9%)	26 (3.9%)

6.2.1 *Serious Adverse Events*

In the Ph3DB study, treatment-emergent serious adverse events (SAEs) were reported in a smaller percentage of subjects in the 300/300-mg and 300/100-mg groups compared with the placebo group, respectively, as follows: 3.5% and 2.0% vs. 5.0% (Table 20). No pattern with respect to the type of event was evident, as all SAEs by PT were reported in ≤ 1% of subjects across treatment groups. Gunshot wound (300/300 mg, n=1), pulmonary embolism (300/100 mg, n=1), drug withdrawal syndrome (300/300 mg, n=2; placebo, n=1) and extradural abscess (placebo, n=1 group) resulted in discontinuation of study treatment.

Table 20: Serious TEAEs in the Ph3DB Study

Preferred Term	RBP-6000 300/300 mg (N=201)	RBP-6000 300/100 mg (N=203)	Placebo (N=100)	RBP-6000 Total (N=404)
Subjects with any serious TEAE	7 (3.5%)	4 (2.0%)	5 (5.0%)	11 (2.7%)
Gunshot wound	2 (1.0%)	0	0	2 (0.5%)
Asthma	0	1 (0.5%)	1 (1.0%)	1 (0.2%)
Pulmonary embolism	0	1 (0.5%)	0	1 (0.2%)
Hernia	1 (0.5%)	0	0	1 (0.2%)
Abscess limb	1 (0.5%)	0	0	1 (0.2%)
Acute myocardial infarction	0	1 (0.5%)	0	1 (0.2%)
Food poisoning	1 (0.5%)	0	0	1 (0.2%)
Cholelithiasis	1 (0.5%)	0	0	1 (0.2%)
Neuroendocrine carcinoma	0	1 (0.5%)	0	1 (0.2%)
Myelomalacia	1 (0.5%)	0	0	1 (0.2%)
Renal impairment	1 (0.5%)	0	0	1 (0.2%)
Hypotension	1 (0.5%)	0	0	1 (0.2%)
Accidental overdose	0	0	1 (1.0%)	0
Drug withdrawal syndrome	0	0	1 (1.0%)	0
Extradural abscess	0	0	1 (1.0%)	0
Suicidal ideation	0	0	1 (1.0%)	0

In the Ph3OL study, serious TEAEs were reported in 3.9% of subjects overall (de-novo: 4.1%; roll-over: 3.5%) (Table 21). No pattern with respect to the type of event was evident as all SAEs by PT were reported in ≤ 1% of subjects across subject groups. Gallbladder perforation (de-novo

group, n=1) and accidental overdose (with benzodiazepine; de-novo group, n=1) resulted in discontinuation of study treatment.

Table 21: Serious TEAEs in the Ph3OL Study

Preferred Term, n (%)	RBP-6000 300/Flex		
	De-novo (N=412)	Roll-over (N=257)	Total (N=669)
Subjects with any serious TEAEs	17 (4.1%)	9 (3.5%)	26 (3.9%)
Cellulitis	3 (0.7%)	1 (0.4%)	4 (0.6%)
Abscess limb	1 (0.2%)	1 (0.4%)	2 (0.3%)
Accidental overdose	2 (0.5%)	0	2 (0.3%)
Asthma	1 (0.2%)	1 (0.4%)	2 (0.3%)
Appendicitis	0	1 (0.4%)	1 (0.1%)
Escherichia pyelonephritis	0	1 (0.4%)	1 (0.1%)
Laceration	1 (0.2%)	0	1 (0.1%)
Localised infection	1 (0.2%)	0	1 (0.1%)
Pneumonia viral	1 (0.2%)	0	1 (0.1%)
Prostatic abscess	1 (0.2%)	0	1 (0.1%)
Staphylococcal bacteraemia	1 (0.2%)	0	1 (0.1%)
Urinary tract infection	1 (0.2%)	0	1 (0.1%)
Arthropod bite	1 (0.2%)	0	1 (0.1%)
Multiple fractures	1 (0.2%)	0	1 (0.1%)
Road traffic accident	1 (0.2%)	0	1 (0.1%)
Thermal burn	0	1 (0.4%)	1 (0.1%)
Adjustment disorder with mixed anxiety and depressed mood	0	1 (0.4%)	1 (0.1%)
Bipolar I disorder	1 (0.2%)	0	1 (0.1%)
Major depression	0	1 (0.4%)	1 (0.1%)
Chronic obstructive pulmonary disease	1 (0.2%)	0	1 (0.1%)
Dizziness	1 (0.2%)	0	1 (0.1%)
Generalised tonic-clonic seizure	0	1 (0.4%)	1 (0.1%)
Myocardial infarction	0	1 (0.4%)	1 (0.1%)
Abdominal pain	1 (0.2%)	0	1 (0.1%)
Gallbladder perforation	1 (0.2%)	0	1 (0.1%)
Hypokalaemia	1 (0.2%)	0	1 (0.1%)
Thrombophlebitis superficial	1 (0.2%)	0	1 (0.1%)

6.2.2 *Deaths*

There was 1 fatal SAE report (gunshot wound) in the RBP-6000 clinical development program as of the NDA data cut-off date. The subject was in the Ph3DB study and received 2 injections of RBP-6000 300 mg. The death was declared a homicide by police and was considered unrelated to study treatment by the investigator. A full narrative is included in Appendix 10.4.

6.2.3 *TEAEs Leading to Study Discontinuation*

In the Ph3DB study, TEAEs that led to discontinuation of study treatment were reported in a small and similar percentage of subjects in the 300/300-mg and 300/100-mg groups compared with the placebo group (5.0% and 3.4% versus 2.0%, respectively; Table 22). No individual TEAE (by PT) led to study treatment discontinuation for more than 1% of subjects in any group.

Table 22: TEAEs that Led to Study Treatment Discontinuation in the Ph3DB Study

Preferred Term, n (%)	RBP-6000 300/300 mg (N=201)	RBP-6000 300/100 mg (N=203)	Placebo (N=100)	RBP-6000 Total (N=404)
Subjects with any TEAE leading to study treatment discontinuation	10 (5.0%)	7 (3.4%)	2 (2.0%)	17 (4.2%)
Drug withdrawal syndrome	0	2 (1.0%)	1 (1.0%)	2 (0.5%)
Aspartate aminotransferase increased	2 (1.0%)	0	0	2 (0.5%)
Sedation	1 (0.5%)	1 (0.5%)	0	2 (0.5%)
Injection site ulcer	1 (0.5%)	0	0	1 (0.2%)
Alanine aminotransferase increased	1 (0.5%)	0	0	1 (0.2%)
Gamma-glutamyltransferase increased	1 (0.5%)	0	0	1 (0.2%)
Liver function test abnormal	1 (0.5%)	0	0	1 (0.2%)
Neutrophil count decreased	1 (0.5%)	0	0	1 (0.2%)
Formication	1 (0.5%)	0	0	1 (0.2%)
Somnolence	1 (0.5%)	0	0	1 (0.2%)
Constipation	0	1 (0.5%)	0	1 (0.2%)
Nausea	1 (0.5%)	0	0	1 (0.2%)
Vomiting	1 (0.5%)	0	0	1 (0.2%)
Hepatitis C	1 (0.5%)	0	0	1 (0.2%)
Lymphadenitis	0	1 (0.5%)	0	1 (0.2%)
Gunshot wound	1 (0.5%)	0	0	1 (0.2%)
Pulmonary embolism	0	1 (0.5%)	0	1 (0.2%)
Rash	0	1 (0.5%)	0	1 (0.2%)
Extradural abscess	0	0	1 (1.0%)	0

In the Ph3OL study, TEAEs that led to study treatment discontinuation were reported in 2.2% of subjects overall (de-novo: 2.7%, roll-over: 1.6%; Table 23). No individual TEAE led to study treatment discontinuation for more than 1% of subjects in any treatment/subject group.

Table 23: TEAEs that Led to Study Treatment Discontinuation in the Treatment Phase of the Ph3OL Study

	RBP-6000 300/Flex		
Preferred Term, n (%)	De-novo (N=412)	Roll-over (N=257)	Total (N=669)
Subjects with any TEAEs leading to study treatment discontinuation	11 (2.7%)	4 (1.6%)	15 (2.2%)
Drug withdrawal syndrome	3 (0.7%)	0	3 (0.4%)
Injection site pain	0	1 (0.4%)	1 (0.1%)
Injection site reaction	1 (0.2%)	0	1 (0.1%)
Injection site swelling	0	1 (0.4%)	1 (0.1%)
Aspartate aminotransferase increased	1 (0.2%)	0	1 (0.1%)
Liver function test abnormal	1 (0.2%)	0	1 (0.1%)
Weight decreased	0	1 (0.4%)	1 (0.1%)
Migraine	0	1 (0.4%)	1 (0.1%)
Sedation	0	1 (0.4%)	1 (0.1%)
Somnolence	1 (0.2%)	0	1 (0.1%)
Constipation	1 (0.2%)	0	1 (0.1%)
Gallbladder perforation	1 (0.2%)	0	1 (0.1%)
Accidental overdose	1 (0.2%)	0	1 (0.1%)
Diabetes mellitus	1 (0.2%)	0	1 (0.1%)

6.2.4 *TEAEs Leading to Dose Reduction*

Dose reductions were not permitted in the Ph3DB study.

In the Ph3OL study, as of the data cut-off date, there were 46 subjects (6.9%) overall that reported a total of 59 TEAEs leading to dose reduction (from 300 mg to 100 mg); 29 subjects (6.8%) in the de-novo group and 17 subjects (6.6%) in the roll-over group. The most common TEAEs leading to dose reduction were elevated liver enzymes, sedation/lethargy/somnolence (related to CNS depression), constipation, nausea and fatigue (Table 24). None of the TEAEs leading to dose reduction were SAEs. At the time of the data cut-off, most of the events (42 of the 59) had resolved or were resolving.

Of the 46 subjects who had dose reductions due to TEAEs, 15 completed the study, 4 withdrew themselves, 3 were withdrawn due to TEAEs, 1 was withdrawn due to pregnancy and the remaining 23 subjects were still ongoing in the study. Of the 15 subjects who completed the study, 13 completed the study at the 100-mg dose.

Table 24: TEAEs Leading to RBP-6000 Dose Reduction in the Ph3OL Study

Preferred Term, n (%)	RBP-6000 300/Flex		
	De-novo[b] (N=412)	Roll-over (N=257)	Total (N=669)
Any TEAE leading to dose reduction	28 (6.8%)	17 (6.6%)	45 (6.7%)
Sedation	2 (0.5%)	5 (1.9%)	7 (1.0%)
Alanine aminotransferase increased[a]	5 (1.2%)	1 (0.4%)	6 (0.9%)
Constipation	4 (1.0%)	1 (0.4%)	5 (0.7%)
Nausea	3 (0.7%)	1 (0.4%)	4 (0.6%)
Fatigue	2 (0.5%)	2 (0.8%)	4 (0.6%)
Aspartate aminotransferase increased[a]	3 (0.7%)	1 (0.4%)	4 (0.6%)
Headache	3 (0.7%)	0	3 (0.4%)
Lethargy	2 (0.5%)	1 (0.4%)	3 (0.4%)
Somnolence	3 (0.7%)	0	3 (0.4%)
Injection site pain	1 (0.2%)	1 (0.4%)	2 (0.3%)
Hepatic function abnormal[a]	2 (0.5%)	0	2 (0.3%)
Gamma-glutamyltransferase increased	1 (0.2%)	1 (0.4%)	2 (0.3%)
Hepatic enzyme increased[a]	1 (0.2%)	1 (0.4%)	2 (0.3%)
Insomnia	2 (0.5%)	0	2 (0.3%)
Therapy change	2 (0.5%)	0	2 (0.3%)
Decreased appetite	0	1 (0.4%)	1 (0.1%)
Muscle twitching	0	1 (0.4%)	1 (0.1%)
Dizziness	0	1 (0.4%)	1 (0.1%)
Hypersomnia	1 (0.2%)	0	1 (0.1%)
Migraine	1 (0.2%)	0	1 (0.1%)
Euphoric mood	1 (0.2%)	0	1 (0.1%)
Erectile dysfunction	0	1 (0.4%)	1 (0.1%)
Flushing	0	1 (0.4%)	1 (0.1%)

a. A total of 10 subjects had a dose reduction because of a PT indicating an increase in liver enzymes.
Note that a subject with more than 1 TEAE leading to dose reduction is counted in the row for each preferred term.
b. 1 subject in the de-novo group was not counted in the table. The subject had an AE of vomiting.

6.3 Injection Site Reactions

Section 6.3.1 provides information on all injection site reactions that were reported as TEAEs. In addition, injection site tolerability assessments were performed for all injections in the Phase 3 studies (Section 6.3.2).

6.3.1 *Injection Site TEAEs*

Across all Phase 3 RBP-6000 subjects overall, 16.5% had at least 1 injection site reaction TEAE (Table 25). Preferred terms for injection site reaction TEAEs in at least 1.0% of subjects were the following: injection site pain (7.2%), injection site pruritus (6.6%), injection site erythema (4.7%), and injection site induration (1.4%). No injection site reaction TEAE was reported as serious. Injection site reaction TEAEs led to study treatment discontinuation for < 1% of subjects in either Phase 3 study.

In the Ph3DB study, larger percentages of subjects who received RBP-6000 reported at least 1 injection site reaction TEAE compared with those who received placebo (300/300-mg 18.9% and 300/100-mg 13.8% vs. placebo 9.0%).

Table 25: Injection Site TEAEs at Any Assessed Time Point in the Phase 3 Studies

Preferred term, n (%)	13-0001 (Ph3DB)			13-0003 (Ph3OL)				All Phase 3
				Roll–over			De-novo	
	RBP-6000 300/300 (N = 201)	RBP-6000 300/100 (N = 203)	Placebo (N = 100)	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)	Total RBP-6000 (N=848)
Any TEAE	38 (18.9%)	28 (13.8%)	9 (9.0%)	6 (5.3%)	13 (11.6%)	2 (6.3%)	61 (14.8%)	140 (16.5%)
Injection site pain	12 (6.0%)	10 (4.9%)	3 (3.0%)	4 (3.5%)	2 (1.8%)	2 (6.3%)	33 (8.0%)	61 (7.2%)
Injection site pruritus	19 (9.5%)	13 (6.4%)	4 (4.0%)	2 (1.8%)	6 (5.4%)	1 (3.1%)	17 (4.1%)	56 (6.6%)
Injection site erythema	6 (3.0%)	9 (4.4%)	0	1 (0.9%)	4 (3.6%)	0	21 (5.1%)	40 (4.7%)
Injection site induration	2 (1.0%)	2 (1.0%)	0	0	1 (0.9%)	0	7 (1.7%)	12 (1.4%)
Injection site bruising	2 (1.0%)	2 (1.0%)	0	0	0	0	2 (0.5%)	6 (0.7%)
Injection site swelling	1 (0.5%)	2 (1.0%)	0	1 (0.9%)	1 (0.9%)	0	1 (0.2%)	6 (0.7%)
Injection site discomfort	1 (0.5%)	1 (0.5%)	0	0	0	0	3 (0.7%)	5 (0.6%)
Injection site reaction	1 (0.5%)	0	0	0	3 (2.7%)	0	1 (0.2%)	5 (0.6%)
Injection site cellulitis	0	1 (0.5%)	0	0	0	0	2 (0.5%)	3 (0.4%)
Injection site infection	1 (0.5%)	0	1 (1.0%)	0	0	0	2 (0.5%)	3 (0.4%)
Injection site dermatitis	0	0	0	0	1 (0.9%)	0	0	1 (0.1%)
Injection site haematoma	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Injection site haemorrhage	1 (0.5%)	0	0	0	0	0	0	1 (0.1%)
Injection site mass	1 (0.5%)	0	0	0	0	0	0	1 (0.1%)
Injection site nodule	1 (0.5%)	0	0	0	0	0	0	1 (0.1%)
Injection site oedema	1 (0.5%)	0	0	0	0	0	0	1 (0.1%)
Injection site rash	1 (0.5%)	0	0	0	0	0	0	1 (0.1%)
Injection site ulcer	1 (0.5%)	0	0	0	0	0	0	1 (0.1%)
Injection site warmth	0	1 (0.5%)	0	0	0	0	0	1 (0.1%)
Injection site inflammation	0	0	1 (1.0%)	0	0	0	0	0

6.3.2 *Injection Site Tolerability Assessments*

6.3.2.1 *Local Injection Site Assessments*

Local injection site assessments were graded by the investigator or a trained and qualified HCP blinded to study treatment. Injection sites were assessed for pain, tenderness, erythema/redness, induration or swelling and each modality was assigned a severity grade of none (Grade 0), mild (Grade 1), moderate (Grade 2), severe (Grade 3) or potentially life-threatening (Grade 4) using an objective assessment scale (Table 26).

Table 26: Injection Site Assessment Scale

Injection Site Reactions	None (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	None	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/Redness[a] (quantitative)	None	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration[b]	None	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Swelling[b] (subjective)	None	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

a. In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
b. Induration/Swelling should have been evaluated and graded using the functional scale as well as the actual measurement.

The most common severities for local injection site tolerability grading for pain, tenderness, induration, erythema/redness or swelling at any assessed time point during the study in all 3 treatment groups were either none or mild. In general, injection site findings of pain, induration, erythema/redness and swelling were reported most commonly with the first injection and decreased in frequency with subsequent injections in all 3 treatment groups. The percentage of subjects with tenderness was generally similar at each of injections #1 through #6 for all 3 treatment groups. Table 27 provides a summary of injection site grading assessments of moderate or severe intensity (note: no injection site assessments were assigned Grade 4 [potentially life-threatening] in the Phase 3 studies).

Table 27: Injection Site Tolerability (Grades Moderate or Severe) at Any Assessed Time Point in the Phase 3 Studies

Assessment, n (%)	Intensity[a] (Grade)	13-0001 (Ph3DB)			13-0003 (Ph3OL)				All Phase 3
					Roll–over			De-novo	
		RBP-6000 300/300 (N = 201)	RBP-6000 300/100 (N = 203)	Placebo (N = 100)	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)	Total RBP-6000 (N=848)
Erythema/redness	Moderate	28 (13.9%)	19 (9.4%)	7 (7.0%)	12 (10.6%)	11 (9.8%)	1 (3.1%)	29 (7.0%)	91 (10.7%)
	Severe	3 (1.5%)	0	1 (1.0%)	0	0	0	5 (1.2%)	8 (0.9%)
Induration	Moderate	21 (10.4%)	6 (3.0%)	3 (3.0%)	4 (3.5%)	5 (4.5%)	1 (3.1%)	10 (2.4%)	44 (5.2%)
	Severe	0	1 (0.5%)	0	0	0	0	3 (0.7%)	4 (0.5%)
Pain	Moderate	19 (9.5%)	16 (7.9%)	11 (11.0%)	5 (4.4%)	3 (2.7%)	1 (3.1%)	24 (5.8%)	66 (7.8%)
	Severe	4 (2.0%)	0	0	0	0	0	4 (1.0%)	8 (0.9%)
Swelling	Moderate	16 (8.0%)	10 (4.9%)	3 (3.0%)	2 (1.8%)	6 (5.4%)	0	8 (1.9%)	37 (4.4%)
	Severe	2 (1.0%)	1 (0.5%)	0	0	0	0	1 (0.2%)	4 (0.5%)
Tenderness	Moderate	52 (25.9%)	45 (22.2%)	28 (28.0%)	18 (15.9%)	12 (10.7%)	9 (28.1%)	83 (20.1%)	199 (23.5%)
	Severe	9 (4.5%)	8 (3.9%)	5 (5.0%)	3 (2.7%)	2 (1.8%)	0	16 (3.9%)	37 (4.4%)

Maximum severity (grade) is reported so that each subject is counted only once at the maximum reported severity for that assessment. All other injection site reactions were rated as grade "none" or "mild".

a. No injection site objective assessment was assigned an intensity of potentially life-threatening (Grade 4) in the Phase 3 studies.

6.3.2.2 *Subject-Reported Injection Site Pain (VAS)*

Subject-reported injection site pain was also assessed in the Phase 3 studies using a 100-mm VAS scale where 0 represented "no pain" and 100 represented "maximum pain". Table 28 provides a representative summary of injection site pain with the first SC injection in the Ph3DB study over time as well as the worst pain reported at any time point through 120 minutes. Subjects reported average pain scores of 40 to 47 across all groups in the first minute after injection. Average pain scores fell considerably after the first minute post-injection. With subsequent injections, the average pain scores declined compared to the first injection.

Table 28: Summary of Local Injection Site Visual Analog Scale (VAS) Pain Scores after the First Injection in the Ph3DB Study

Minutes Post-Injection	Statistics	RBP-6000 300/300 mg (N=201)	RBP-6000 300/100 mg (N=203)	Placebo (N=100)	RBP-6000 Total (N=404)
1 minute	Mean (SD) Median	43 (30) 43	40 (27) 40	47 (31) 44	42 (29) 41
5 minutes	Mean (SD) Median	14 (20) 5	12 (18) 4	23 (25) 13	13 (19) 4
10 minutes	Mean (SD) Median	8 (17) 1	7 (12) 1	14 (20) 5	7 (14) 1
30 minutes	Mean (SD) Median	3 (8) 0	3 (7) 0	8 (17) 1	3 (8) 0
60 minutes	Mean (SD) Median	4 (12) 0	1 (3) 0	3 (7) 0	3 (9) 0
120 minutes	Mean (SD) Median	2 (6) 0	2 (5) 0	3 (9) 0	2 (5) 0
Worst pain at any time through 120 minutes	Mean (SD) Median	43 (30) 43	41 (27) 40	47 (31) 49	42 (29) 41

6.4 Depot Removal

There were 2 reports of surgical removal of the RBP-6000 depot in the clinical program. One subject in the opioid blockade study had the depot removed (study day 13) after withdrawing consent and requesting removal of the depot. One subject in a Phase 1 study (Study 13-0006) had the RBP-6000 depot removed (study day 16) due to an SAE of abnormal liver chemistry values. The subject subsequently tested positive for hepatitis C within 1 month of the liver enzyme elevation. No complications were reported following the RBP-6000 depot removal for either subject.

No RBP-6000 depots were surgically removed in the Phase 3 studies. There were also no reports of attempted depot removal by subjects in the Phase 3 studies.

6.5 Electrocardiograms

As part of the RBP-6000 development program, extensive cardiac monitoring was performed. A medical review of all 7 studies of RBP-6000 (over 30,000 electrocardiograms [ECGs] in the clinical database) provided no evidence for buprenorphine-induced QT prolongation, syncope, seizure, or ventricular tachycardia or fibrillation.

In the pooled Phase 3 studies, mean values were within the normal references ranges for heart rate, QRS, QT, QTcF, QTcB, RR and PR at all time points. In the Ph3DB study, the incidence of TEAEs pertaining to ECGs and cardiac disorders were was low (≤ 2% by PT) and similar between RBP-6000 and placebo; in the Ph3OL study, these TEAEs were reported for ≤ 1% of subjects overall.

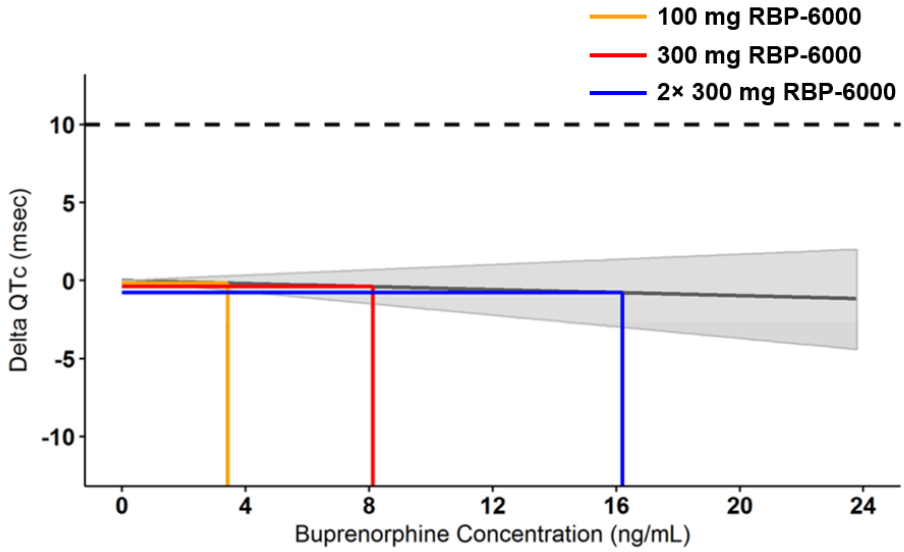
In addition, the Ph3DB study included robust ECG assessments time-matched with PK sampling to ascertain whether RBP-6000 influences cardiac repolarization. A combination of triplicate ECGs at screening, single 12-lead ECGs on non-dosing days and triplicate readings from Holter monitoring on dosing days were collected. When Holter monitoring was available, specific 12-lead ECG tracings of 10 seconds' duration were extracted in triplicate prior to SC injection and at 4 and 24 hours post-SC injection on each dosing day. Holter and non-Holter data were centrally read.

As a consequence of this extensive cardiac monitoring through the RBP-6000 clinical program, a comprehensive clinical cardiac safety database and a concentration-QT profile based on nearly 12,000 time-matched ECG and PK data in more than 1100 subjects with OUD were compiled. From the profile, a concentration-QT model was developed using pooled plasma concentration-ECG data across 5 studies (Ph3DB, MAD, SAD, MW, and first-time-in-humans [FTIH]).

Many of the concomitant medications or illicit drugs taken by OUD subjects have the potential to affect QT and heart rate. Because these concomitant medications were recorded in the clinical studies of RBP-6000, and illicit opioid use was assessed through UDS and self-reports, these effects on heart rate and QT interval were accounted for in the modeling prior to establishing a baseline QTc and determining whether there was a drug-related effect of buprenorphine on QT.

There was a small non-positive related effect of buprenorphine on QT with the upper 90% confidence interval for the predicted mean under 10 msec after repeated (monthly) SC injections of 100-mg RBP-6000, 300-mg RBP-6000, and at 2-fold higher than clinically observed concentrations in Ph3DB study at 300-mg (Figure 26). An effect of RBP-6000 on QT can be ruled out at therapeutic concentrations as well as supratherapeutic doses (i.e., 2-fold higher than those associated with the maximum clinical dose of 300 mg), after accounting for the covariates that may influence heart rate and QT in patients with OUD.

Figure 26: Predicted Mean (90% CI) Delta QTc at Concentration Levels Corresponding to Repeated Monthly Doses of 100-mg, 300-mg, and 2× 300-mg (600 mg) RBP-6000



6.6 Liver Chemistry

Elevated hepatic enzymes are consistent with the known safety profile of buprenorphine for OUD (Saxon et al. 2013; Fareed et al. 2014) and were expected with RBP-6000.

A summary of results from liver chemistry in the Ph3DB and Ph3OL studies is provided in Table 29. In the Ph3DB study, the incidence of ALT more than 3 times the upper limit of normal (> 3 × ULN) was 12.4%, 5.4%, and 4.0% in the RBP-6000 300/300-mg, RBP-6000 300/100-mg, and placebo groups, respectively. The incidence of AST > 3 × ULN was 11.4%, 7.9%, and 1.0%, respectively. The incidence of total bilirubin > 2 × ULN was 0.5%, 0.5%, and 0%, respectively. The incidence rates of elevated liver enzymes in the roll-over and de-novo group in the Ph3OL study were generally consistent with those observed in the active groups of the Ph3DB study. Importantly, no SAEs potentially pertaining to liver dysfunction and no potential Hy's Law cases occurred in any subject in the clinical program.

Table 29: Liver Chemistry Results in the Phase 3 Studies

Liver Chemistry Result, n (%)	13-0001 (Ph3DB)			13-0003 (Ph3OL)				All Phase 3
				Roll–over			De-novo	
	RBP-6000 300/300 (N = 201)	RBP-6000 300/100 (N = 203)	Placebo (N = 100)	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)	Total RBP-6000 (N=848)
ALT								
> 3 × ULN to < 5 × ULN	18 (9.0%)	6 (3.0%)	2 (2.0%)	8 (7.1%)	4 (3.6%)	0	22 (5.3%)	49 (5.8%)
≥ 5 × ULN to < 8 × ULN	3 (1.5%)	3 (1.5%)	1 (1.0%)	1 (0.9%)	3 (2.7%)	1 (3.1%)	16 (3.9%)	26 (3.1%)
≥ 8 × ULN	4 (2.0%)	2 (1.0%)	1 (1.0%)	2 (1.8%)	1 (0.9%)	1 (3.1%)	13 (3.2%)	23 (2.7%)
AST								
> 3 × ULN to < 5 × ULN	15 (7.5%)	10 (4.9%)	0	4 (3.5%)	7 (6.3%)	1 (3.1%)	24 (5.8%)	52 (6.1%)
≥ 5 × ULN to < 8 × ULN	4 (2.0%)	3 (1.5%)	0	6 (5.3%)	5 (4.5%)	0	7 (1.7%)	23 (2.7%)
≥ 8 × ULN	4 (2.0%)	3 (1.5%)	1 (1.0%)	0	1 (0.9%)	1 (3.1%)	14 (3.4%)	23 (2.7%)
ALT & AST								
> 3 × ULN to < 5 × ULN	7 (3.5%)	5 (2.5%)	0	4 (3.5%)	4 (3.6%)	0	13 (3.2%)	29 (3.4%)
≥ 5 × ULN to < 8 × ULN	1 (0.5%)	0	0	1 (0.9%)	3 (2.7%)	0	3 (0.7%)	8 (0.9%)
≥ 8 × ULN	4 (2.0%)	2 (1.0%)	1 (1.0%)	0	0	1 (3.1%)	8 (1.9%)	15 (1.8%)
Total Bilirubin								
> 2 × ULN to < 5 × ULN	1 (0.5%)	1 (0.5%)	0	0	0	0	4 (1.0%)	6 (0.7%)[a]
≥ 5 × ULN	0	0	0	0	0	0	1 (0.2%)[b]	1 (0.1%)[b]
Potential Hy's Law Case	0	0	0	0	0	0	0	0

[a] All 6 of these subjects had cholelithiasis.
[b] Subject had hepatitis A.

The incidence of ALT and AST elevations in the Ph3DB study was also similar to that in a 24-week safety study with SUBOXONE that was conducted by the National Institute of Drug Abuse (NIDA) in 2006. As shown in Table 30, the incidence of ALT and AST elevations at the same visit and bilirubin elevations were similar for RBP-6000 and SUBOXONE.

Table 30: Liver Chemistry Results in Ph3DB Study of RBP-6000 and in Hepatic Safety Study of SUBOXONE

	Phase 3 Double-Blind		NIDA Study[1]
Liver Chemistry Result, n (%)	RBP-6000 300/300 mg N=201	RBP-6000 300/100 mg N=203	SUBOXONE N=635
ALT & AST at same visit			
> 3 × ULN to < 5 × ULN	7 (3.5%)	5 (2.5%)	21 (3.4%)
≥ 5 × ULN to < 8 × ULN	1 (0.5%)	0	13 (2.1%)
≥ 8 × ULN	4 (2.0%)	2 (1.0%)	6 (1.0%)
Total Bilirubin > 2 × ULN	1 (0.5%)	1 (0.5%)	2 (0.3%)

[1]NIDA CTN-0027 Final Report

Medical review of the 27 subjects in the Ph3DB study and 55 subjects in the Ph3OL study who had ALT and AST > 3 × ULN at any time found that most of these cases (24 and 35, respectively) had clinical factors associated with liver chemistry elevations such as hepatitis C, chronic alcohol use, history of alcoholic hepatitis/pancreatitis, or elevated liver chemistry values at screening or baseline.

A recognized method for organizing and evaluating liver safety is evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plots. eDISH plots organize liver chemistry data graphically by plotting peak serum total bilirubin values on peak ALT or AST values. Peak ALT or AST > 3 × ULN with total bilirubin > 2 × ULN is considered a potential Hy's Law case (i.e., actual Hy's Law cases denote severe drug-induced liver injury [DILI] if it is confirmed that no other reason can be found to explain the combination of increased aminotransferase and total bilirubin). These plots are provided in Appendix 10.5.

Exposure-response analyses were conducted to evaluate the relationship between buprenorphine plasma concentration and the probability of elevations in ALT or AST (> 3 × ULN, > 5 × ULN, and > 8 × ULN) with RBP-6000 in the Phase 3 studies. Overall, exposure-response curves were flat within the observed concentration range, which did not suggest a relationship between buprenorphine exposure and liver chemistry elevations.

Given the known effects of buprenorphine on liver chemistry and the fact that patients with OUD are at high risk for pre-existing liver disease (e.g., hepatitis B, C, and D; human immunodeficiency virus [HIV]; alcohol-induced liver disease), Indivior is proposing that the label for RBP-6000 include the same recommendations addressing hepatic safety as the current label for SUBOXONE. These recommendations include conducting a baseline assessment of liver chemistry, periodic monitoring of liver chemistry, and searching for an etiology should liver chemistry values rise.

In summary, consistent with the known hepatic safety profile of buprenorphine, the incidence of TEAEs potentially associated with hepatic disorders was higher in subjects treated with RBP-6000 compared with subjects treated with placebo. A thorough review of data on hepatic safety, including both TEAEs and results of liver chemistry values, and exposure-response analyses for elevations in liver chemistry values, found no evidence of drug-induced liver damage with RBP-6000. No new signal indicative of hepatic injury was observed during long-term use of RBP-6000.

6.7 Respiratory Depression and RBP-6000 Overdose

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

6.8 Overdose with Other Drugs

In the Ph3DB study, 1 subject in the placebo group had a non-fatal accidental heroin overdose.

In the Ph3OL study, 1 subject had a non-fatal accidental heroin overdose. Another subject had a non-fatal accidental overdose with ingestion of multiple diazepam tablets (UDS positive for multiple substances) with study treatment withdrawn. Another subject had suspected overdose of trazadone. The trazadone overdose was not considered to be treatment-emergent since it occurred after completion of the safety follow-up period.

6.9 Safety by Subgroup

No adjustments regarding individualizing therapy or patient management are warranted based on subgroup evaluations of TEAE reports by sex, age, race, BMI, baseline severity of OUD, lifetime history of OUD, geographic region, or use of opioids by the IV route in the Ph3DB study.

6.10 Safety Conclusions

The safety profile of buprenorphine for the treatment of OUD is well known and established. Though buprenorphine is not without risk, it is important to consider those risks relative to the substantial benefits to patients with OUD, particularly reducing the use of illicit opioids and therefore the risk of fatal overdose. The primary goal of the safety analyses for the Phase 3 program for RBP-6000 was to characterize its safety profile and to compare it to the known safety profile of currently-approved buprenorphine products.

Both dosing regimens of RBP-6000 in the Ph3DB study and flex dosing in the Ph3OL study were demonstrated to be safe and well-tolerated, with many of the subjects remaining in treatment for the length of the studies, which was up to 12 months. There were no new safety signals identified beyond what is known from the safety profiles of FDA-approved buprenorphine products, with the exception of anticipated local injection site reactions, which were generally transient, mild or moderate in severity, and self-limiting. No injection site reaction TEAEs were reported as serious, and injection site reaction TEAEs led to discontinuation in < 1% of subjects in either Phase 3 study.

7 RISK EVALUATION AND MITIGATION STRATEGY (REMS) FOR RBP-6000

Summary

- Indivior is proposing a REMS to promote safe and appropriate use of RBP-6000.
- The primary goals of the REMS will be to mitigate the risks of diversion, misuse, abuse, and accidental exposure; and, to inform prescribers, pharmacists, and patients about the long-acting nature of RBP-6000 as well as its risks.
- The REMS for RBP-6000 uses elements similar to those in the REMS for SUBOXONE SL film, but also includes a restricted distribution system to limit diversion.
- Key components of the REMS include the distribution of physician and patient education materials; surveillance monitoring for diversion, misuse, and abuse; adverse event monitoring; intervention strategies to identify noncompliance and to work with local communities and to develop specific plans of action in cases where there are concerning levels of misuse or abuse; and, regular assessments of the REMS effectiveness in achieving its goals.

7.1 Background

As a buprenorphine product, RBP-6000 will be a Schedule III narcotic under the Controlled Substances Act (CSA). Risk management efforts are in place as a result of the Drug Addiction Treatment Act of 2000 (DATA-2000). DATA-2000 has made treatment for OUD more available by permitting qualified physicians to prescribe Schedule III, IV, or V narcotics specifically approved by FDA for the treatment of opioid dependence in an office-based setting.

Under the CSA, physicians submit an application (Notice of Intent) and certify that they will prescribe only those medications approved by FDA for the treatment of opioid dependence. Physicians also certify that they will treat a limited number of patients and that they have the capacity to refer patients for counseling and other necessary services. In 2016, the Comprehensive Addiction and Recovery Act (CARA) was passed, extending prescribing authority to nurse practitioners and physician assistants.

To ensure that prescribers have met the qualifications to prescribe buprenorphine-containing products for opioid dependence, the Drug Enforcement Administration (DEA) requires prescribers to include a unique identifier on each prescription written for these products. The DEA also has the authority to audit a DATA-2000-waivered prescriber to monitor for diversion by reviewing compliance with security and recordkeeping requirements.

If approved, RBP-6000 will be added to the list of buprenorphine products eligible for prescribing by DATA-2000-waivered prescribers and prescribers at opioid treatment programs. All these products are subject to a Risk Evaluation and Mitigation Strategy (REMS) to assure that the benefits of buprenorphine treatment outweigh the risks, by minimizing the risk of diversion, misuse, abuse, overdose, and pediatric exposures.

Accordingly, Indivior has proposed a REMS for RBP-6000. The primary elements of the REMS are similar to the existing REMS for SUBOXONE SL film, with the additional element of a restricted distribution system to limit diversion. The primary goals of the RBP-6000 REMS include:

- Mitigating the risks of diversion, misuse, abuse, and accidental exposure
- Informing prescribers, pharmacists, and patients of the risks associated with RBP-6000
- Informing prescribers, pharmacists, and patients about the long-acting nature of RBP-6000

7.2 Considerations in the Design of the RBP-6000 REMS Program

In designing a risk mitigation strategy for RBP-6000, the following were considered: the product formulation, the dose of buprenorphine, the proposed method of administration, the patient population for which treatment is indicated, the laboratory risk assessment of the ability to extract buprenorphine from RBP-6000 for the purposes of abusing buprenorphine through various routes of administration, and the proposed method for product distribution.

RBP-6000 contains 100 mg or 300 mg of buprenorphine base without naloxone, and thereby could be appealing to individuals who inject opioids. Restricted distribution to healthcare settings only and direct administration by a HCP will prevent the product from being in the hands of the patient at any time, therefore minimizing the potential for diversion, misuse, and abuse.

Indivior has studied the RBP-6000 formulation for extractability before and after SC injection for the purpose of assessing abuse via various routes of administration. The results of the analyses are important for evaluating the nature of the risks, should the product be diverted before administration. If RBP-6000 is diverted and manipulated in order to extract buprenorphine prior to administration, there is risk of abuse via IV and intra-arterial injection. There is a lower risk of abuse via SL, insufflation, smoking, or other routes. Further, illicit self-administration poses a more serious risk of harm if injected via the IV route, than by the SC route.

7.3 Product Distribution

Importantly, RBP-6000 will not be distributed to patients by retail pharmacies, and will not be distributed or dispensed to patients directly under any circumstances. Indivior is proposing restricted distribution of the product by specialty pharmacies or specialty distributors, dispensing only in certain healthcare settings, and administration of the product by an HCP to minimize the risks of diversion, misuse, abuse, and accidental overdose.

The specialty pharmacy and specialty distributor channels have been determined to be compliant with the CSA. Restricted distribution requires that drug is dispensed or sold only to prescribers who are DATA-2000-waivered, including but not limited to hospitals, long-term care facilities, prisons, and inpatient psychiatric units. An exception to this would be federally-approved OTPs where the HCP is not required to have a DATA-2000 waiver. Distribution of RBP-6000 from the manufacturer to specialty pharmacies and specialty distributors will be compliant with the CSA and subject to DEA enforcement.

7.4 Objectives of the RBP-6000 REMS Program

The specific objectives to be achieved by the RBP-6000 REMS include the following:

For Patients:

- Inform patients that RBP-6000 cannot be obtained through retail pharmacies.
- Inform patients that RBP-6000 will only be available in certain healthcare settings to be administered by an HCP.
- Inform patients they must first undergo induction with a transmucosal buprenorphine-containing product before being transitioned to RBP-6000.
- Inform patients of the serious risks associated with improper administration of RBP-6000 (e.g., serious harm or death if administered IV).
- Inform patients of the long-acting nature of RBP-6000, and because of this, the risk of increased CNS depression if RBP-6000 is co-administered with opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics, or other CNS depressants (including alcohol).
- Inform patients of the effects of the ATRIGEL Delivery System (i.e., that the patient may have a small lump at the injection site for several weeks that will decrease in size over time).
- Inform patients it is important not to rub or massage the injection site and to be aware of the placement of any belts or clothing waistbands.
- Inform patients to tell all of their HCPs that they are receiving treatment with RBP-6000, particularly in the case of an accident, emergency surgery, or where they need for certain concomitant medications (e.g., CNS depressants) may increase CNS depression.

For Prescribers:

- Inform prescribers that RBP-6000 cannot be obtained through retail pharmacies.
- Inform prescribers that RBP-6000 will only be available in certain healthcare settings to be administered by an HCP.
- Inform prescribers to confirm the patient meets the diagnostic criteria for moderate-to-severe OUD.
- Inform prescribers that they need to confirm the patient has undergone induction on a transmucosal buprenorphine-containing product. The patient may only be transitioned to RBP-6000 after signs and symptoms of opioid withdrawal have been suppressed for a minimum of 24 hours.
- Inform prescribers, that given the long-acting nature of RBP-6000, they should be aware of the following:
    - Patients receiving buprenorphine in the presence of opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers,

sedative/hypnotics, or other CNS depressants (including alcohol) may exhibit increased CNS depression.

- In situations of concomitant prescription of CNS depressants and RBP-6000, prescribers should consider dose reduction of the CNS depressants.
- Patients with moderate hepatic impairment or who develop moderate-to-severe hepatic impairment while being treated with RBP-6000 should be monitored for several months for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

- Inform prescribers to counsel the patient on the risks of serious harm or death if RBP-6000 is injected IV.
- In situations of concomitant prescription of CNS depressants and RBP-6000, prescribers should consider dose reduction of the CNS depressants.
- Inform prescribers to monitor patients who elect to discontinue RBP-6000 for several months for signs and symptoms of withdrawal and treat the patient appropriately.
- Inform prescribers that patients should be counseled to tell all of their HCPs they are taking RBP-6000.
- Inform prescribers that the Medication Guide and a Patient Alert Card should be provided to the patient when treatment with RBP-6000 is initiated.
- Inform prescribers they should use the Appropriate Use Checklist or another method (e.g., electronic health record) specific to the prescriber's office practice to document conditions of safe use and patient monitoring.

For Pharmacists:

- Inform pharmacists that RBP-6000 cannot be obtained through retail pharmacies.
- Inform pharmacists that RBP-6000 will only be available in certain healthcare settings to be administered by an HCP.
- Inform pharmacists that patients must undergo induction on a transmucosal buprenorphine-containing product. The patient may only be transitioned to RBP-6000 after signs and symptoms of opioid withdrawal have been suppressed for a minimum of 24 hours.
- Inform pharmacists that given the long-acting nature of RBP-6000, they should be aware of the following:
  - Patients receiving buprenorphine in the presence of opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics, or other CNS depressants (including alcohol) may exhibit increased CNS depression.
  - In situations of concomitant prescription of CNS depressants and RBP-6000, prescribers should consider dose reduction of the CNS depressants.
- Patients with moderate hepatic impairment or who develop moderate-to-severe hepatic impairment while being treated with RBP-6000 should be monitored for several months

for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

- Inform pharmacists if RBP-6000 is injected IV, there is a risk of serious harm or death.

7.5 Proposed Elements of the RBP-6000 REMS Program

The REMS for RBP-6000 includes a Medication Guide and Elements to Assure Safe Use (ETASU). The REMS educational tools are provided to ensure safe use of the product and include a *REMS HCP Letter*, *REMS Professional Society Letter*, *Appropriate Use Checklist*, *REMS HCP Brochure*, and a *Patient Alert Card*.

Medication Guide

A Medication Guide will be available for distribution in accordance with federal regulations. Because RBP-6000 will be administered by an HCP in a healthcare setting, the Medication Guide will be provided to the patient at treatment initiation with RBP-6000, and subsequently, if the Medication Guide is changed or the patient requests a copy. The Medication Guide will be packaged with each dose of RBP-6000 and will be available via the RBP-6000 REMS website.

Elements to Assure Safe Use

- **Safe Use Conditions –** RBP-6000 will only be prescribed and administered to patients with documentation of safe use conditions, including:
  - Patient meets the diagnostic criteria for moderate-to-severe OUD
  - Prescriber should confirm induction has been appropriately based on the Prescribing Information (PI)
  - Patient may be transitioned to RBP-6000 only after having undergone induction with a transmucosal buprenorphine-containing product.
  - Prescriber has reminded the patient about the information outlined in Section 7.4 of this document
  - Prescriber should document safe use conditions for each patient by using the *Appropriate Use Checklist*, or by using another method (e.g., electronic health record) specific to the prescriber's office practice
- **Monitoring –** Each patient receiving treatment with RBP-6000 will be subject to the monitoring outlined below. Prescribers will document that each patient has received the required clinical monitoring using the *Appropriate Use Checklist*, or by using another method/system specific to the prescriber's office practice.
  - Return visits are scheduled at intervals commensurate with medical, psychosocial, and other needs as defined in an individualized treatment plan
  - Assessment and reinforcement of the patient's compliance with his/her treatment plan
  - Assessment of the RBP-6000 injection site for signs of infection or evidence of tampering or attempts to remove the depot
  - Assessments of patient for progression of OUD and addictive behaviors

- Assessment of appropriateness of RBP-6000 dosage prescribed depending on tolerability and therapeutic response
- Assessment of concomitant medications
- Assessment of adverse events
- Assessment and documentation of the patient's counseling/psychosocial support. If additional support is needed, the patient should be referred to a qualified provider
- Assessment of whether the patient is making adequate progress toward treatment goals
- Monitor patients who elect to discontinue RBP-6000 for several months for withdrawal and treat the patient appropriately

- **RBP-6000 Dispensed Only in Certain Healthcare Settings –** To minimize the potential for diversion, misuse, abuse, and diversion, RBP-6000 must be administered by an HCP in a healthcare setting. Administering buprenorphine 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, require that the prescriber be DATA-2000-waivered.

  RBP-6000 can also be administered in federally approved OTPs where a DATA-2000 waiver is not required. For this REMS when dispensing to a named patient, specialty pharmacies must coordinate the delivery of RBP-6000 to HCPs with the patient's appointment.

- **REMS Tools -** The following REMS tools will be mailed to relevant parties identified below and will be available via the RBP-6000 REMS website.
  - REMS Prescriber Letter: Upon approval of the RBP-6000 REMS, the letter will be mailed to all prescribers certified to treat opioid dependence under DATA-2000 and to prescribers at OTPs. The letter includes information directed to prescribers consistent with the goals and objectives of the REMS. When the materials update, a letter will be sent to all prescribers describing the changes.
  - REMS Pharmacist Letter: The letter will be mailed to the pharmacists or the appropriate individual in charge at all channel partners that have entered into a contractual agreement with Indivior to dispense and distribute RBP-6000, as well as pharmacists in charge at health-system pharmacies, inpatient pharmacies, and other alternative injection facilities where RBP-6000 may be given that have entered into a contractual agreement with Indivior. The letter includes information directed to pharmacists/appropriate individuals consistent with the goals and objectives of the REMS. The REMS materials will be mailed again if any updates are made to the materials and when any new facilities are identified to dispense, distribute or administer RBP-6000.
  - REMS Professional Society Letter: The letter will be mailed to the leadership of relevant medical societies and associations. The letter includes the same information in the *REMS Prescriber Letter* and the *REMS Pharmacist Letter*. It is directed to the leadership of the societies, asking them to distribute the information to their members.

- Appropriate Use Checklist: The checklist will be mailed to all prescribers certified to treat opioid dependence under DATA-2000 and to prescribers at OTPs. Prescribers and their staff will be instructed to use the *Appropriate Use Checklist* or another method (e.g., electronic health record) specific to the prescriber's office practice for use as documentation of safe use conditions and monitoring. It will be a reminder to the staff about key issues and milestones to discuss during each patient's visit and can be placed in the patient's medical record.
- REMS HCP Brochure: The brochure will be mailed to all prescribers certified to treat dependence under DATA-2000, prescribers at OTPs, and pharmacists/appropriate individuals in charge at all channel partners that have entered into a contractual agreement with Indivior to dispense and distribute RBP-6000, as well as pharmacists/appropriate individuals in charge at health-system pharmacies, inpatient pharmacies, and other alternative injection facilities where RBP-6000 may be administered under contractual agreement with Indivior. It comprehensively outlines the most important safety information about RBP-6000 directed to prescribers and pharmacists, and contains recommendations consistent with those in the goals and objectives of the REMS.
- Patient Alert Card: The cards will be mailed to all prescribers certified to treat opioid dependence under DATA-2000 and prescribers at OTPs. The *Patient Alert Card* is a wallet-size card that prescribers should provide to their patients when initiating therapy with RBP-6000. The purpose of the card is to ensure that a patient has a convenient way of communicating to any HCP caring for them (e.g., in case of an accident or emergency surgery) that they are taking RBP-6000 for moderate-to-severe OUD.
- REMS Website: The RBP-6000 REMS website will be available for use within 60 days of initial approval of the RBP-6000 REMS. All REMS tools and RBP-6000 Prescribing Information and Medication Guide will be available through the RBP-6000 REMS website, except the Professional Society Letter. Updates to the REMS website will be made as appropriate with any Prescribing Information, Medication Guide, or REMS tools changes, as appropriate. Educational resources will also be available for prescribers, pharmacists, and patients on the website.

7.6 Adverse Event Monitoring, Analysis, and Reporting

The activities occurring under this REMS will be integrated with Indivior's pharmacovigilance program to ensure proper surveillance, monitoring, and reporting of adverse events from all sources. Indivior's pharmacovigilance program involves the monitoring for adverse events of special interest, including all reports of overdose, misuse, abuse, elevated liver chemistry values, or hepatic adverse events. Indivior's pharmacovigilance staff will collect as much information as possible about these events in a standardized fashion. The pharmacovigilance program will be implemented through standard operating procedures to ensure a robust, systematic process for capturing, evaluating, investigating, responding to and reporting adverse events. Adverse event reports will be individually reviewed and collectively evaluated to determine if changes to the REMS messages could help to further mitigate the risks.

7.7 Intervention Strategies

Indivior has established strategies to address the need to minimize the risks of RBP-6000. Indivior has personnel who are responsible for overseeing the direction, planning, execution and interpretation of its risk management activities used for evaluating and mitigating the diversion of RBP-6000. Under the direction of Indivior's medical department, Indivior will intervene by working with local communities and developing specific plans of action when there are concerning levels of misuse or abuse of RBP-6000. Indivior will also routinely monitor prescribing behavior to identify noncompliance, and will intervene to ensure adequate processes and procedures are in place.

7.8 Implementation System and Timetable for REMS Assessment

Indivior is committed to evaluating the effectiveness of the REMS for RBP-6000 and reporting the results to FDA. Indivior will monitor compliance with the requirements to document prescribing and dispensing with documentation of safe use conditions and monitoring of patients through surveys of patients and prescribers, evaluations of healthcare utilization databases, and ongoing surveillance (sources including, but not limited to, ongoing pharmacovigilance, internet, street ethnography, national databases, and surveys conducted at substance abuse treatment programs). Indivior will also ensure that channel partners who agree to dispense and distribute RBP-6000 agree to comply with the REMS program and to fill each RBP-6000 prescription as per the REMS requirements.

Indivior will submit REMS Assessments to FDA at 6 months and at 12 months after initial REMS approval, then annually thereafter. The annual assessment reports will include, but are not limited to:

- An analysis and summary of surveillance and monitoring activities for RBP-6000 overdose and misuse and any intervention taken resulting from signals of overdose and misuse
- An analysis to evaluate RBP-6000 utilization patterns including frequency of office visits/patient/prescriber, and other indicators of adherence to practices important for safe use
- An analysis and summary of knowledge, attitudes and behavior surveys of patients and prescribers to assess the understanding of the goals and objectives of the REMS and understanding of the most important risk messages
- An evaluation of implementation of REMS outreach during the assessment period
- A summary of the audits of the Specialty Pharmacies and Specialty Distributors
- An evaluation of the effectiveness of the risk minimization program and recommendations for program improvements or changes, if any are required

The RBP-6000 REMS will undergo periodic review to evaluate the effectiveness of the strategies and tools in accomplishing the goals and objectives of the REMS. These evaluations will inform appropriate revisions to the REMS as necessary. Based on the monitoring and evaluation of these ETASU, Indivior will take reasonable steps to improve implementation of these elements.

8 BENEFIT-RISK ANALYSIS

RBP-6000 is an extended-release formulation of buprenorphine intended to provide a new option to help address the unmet treatment needs of patients with OUD as they work to regain control of their lives. This new delivery system may benefit multiple types of patients, including those who struggle with the need to take a daily medication and those who face the ongoing risk of relapse due to the chronic, relapsing nature of OUD. RBP-6000 has also been designed to reduce the risks of diversion, misuse, abuse, and accidental exposure to buprenorphine among children.

The benefits and risks of RBP-6000 can be considered in terms of both the patient and public health and are summarized in Table 31.

Table 31: Benefit-Risk Analysis of RBP-6000

Patient Benefits	Patient Risks
• Convenience of monthly vs. daily dosing • Reduces adherence burden • Enforces compliance (i.e., remove ability to take "drug holiday") • Opioid blockade from the first dose • Benefits without supplemental buprenorphine	• Adverse events similar to currently-approved oral buprenorphine products • Injection site reactions • Depot requires surgical removal if treatment needs to be discontinued
Public Health Benefits	**Public Health Risks**
• Restricted distribution and administration by HCPs reduces risk of diversion • Depot formulation reduces risks of misuse and abuse • Eliminates risk of accidental pediatric exposure	• Known abuse potential of buprenorphine if product could be diverted

While transmucosal buprenorphine treatments are effective, many treatment-seeking patients who are motivated to stop abusing opioids have difficulty adhering to daily dosing. Not surprisingly, lower adherence to medication is associated with substantially higher likelihood of relapse to illicit opioid use. The monthly dosing schedule with RBP-6000 substantially reduces the burden of adherence for patients. RBP-6000 may help prescribers manage patients more effectively given that they can consider the efficacy of buprenorphine treatment without the question of whether or not a patient is adhering to daily dosing. Furthermore, the depot formulation enforces patient compliance by design, since patients would not be able to take a "drug holiday" by not taking their medication for a day or two so they could get high with an illicit opioid. While these product attributes are expected to provide considerable benefit to patients, if treatment needs to be discontinued, the depot would have to be surgically removed.

RBP-6000 provides sustained buprenorphine plasma exposure over the monthly dosing interval, with less fluctuation in buprenorphine plasma concentrations than with transmucosal formulations. The clinical program for RBP-6000 has demonstrated that RBP-6000 delivers effective opioid blockade from the first dose without the need for supplemental buprenorphine. Thus, RBP-6000 optimizes the delivery of buprenorphine by providing patients with sustained medication levels that can be expected to impart continued benefit from the medication.

RBP-6000 will be made available in dosage strengths of 300-mg and 100-mg. The recommended dosing regimen for RBP-6000 is 300-mg for the first 2 months followed by maintenance treatment with 100-mg or 300-mg monthly based on the clinical condition of the patient. Allowing providers to use their clinical judgement to select the maintenance dose for their patients is appropriate in the context of prior studies which have demonstrated that certain clinical factors, such as psychiatric comorbidities, the presence of chronic pain, and use of other substances, influence the amount of buprenorphine required to achieve opioid blockade. Furthermore, clinical studies of buprenorphine have shown that injecting drug users have a higher chance of remaining in treatment and achieving abstinence with higher doses of buprenorphine.

Any advance in reducing diversion, misuse, abuse, or accidental pediatric exposure of medical therapy for OUD would benefit the public health. Clinicians acknowledge the potential risks associated with take-home, patient self-administered buprenorphine and methadone MAT. RBP-6000 addresses some of these public health concerns in that it will be administered only by qualified HCPs in a healthcare setting and will be distributed via a carefully controlled supply chain. These measures will make RBP-6000 less prone to diversion compared to products that are dispensed to patients for self-administration. Furthermore, the fact that RBP-6000 is administered via SC injection in a healthcare setting eliminates the potential for accidental exposure among children. The controlled distribution system can also be expected to offset the potential risk of abuse since RBP-6000 is a high dose of buprenorphine that would be attractive for abuse.

Buprenorphine is not without risks. Like any opioid, some patients may experience constipation, nausea, and vomiting, or side effects related to respiratory or CNS depression. Also similar to other opioids, there is a heightened risk of overdose when buprenorphine is co-administered with benzodiazepines or sedative/hypnotics. In addition, buprenorphine has a known impact on liver enzymes which can pose serious issues for individuals who have or develop hepatitis B, C, or E or other hepatic conditions.

The safety profile of RBP-6000 has been shown to be consistent with other transmucosal buprenorphine-containing products, with the exception of injection site reactions, which are expected with injectable therapies. The percentage of subject study discontinuation secondary to an AE was no more than 5% of subjects in any of the Phase 3 studies. Injection site reactions were generally mild or moderate in severity, self-limiting, and led to discontinuation from treatment in fewer than 1% of cases. The hepatic safety profile of RBP-6000 was consistent with the known safety profile of buprenorphine-containing products. The totality of the safety findings suggests that RBP-6000 has a favorable safety profile with regard to the treatment of patients with OUD.

Overall, results from the clinical development program demonstrated that RBP-6000 provided opioid blockade, clinically meaningful benefits – as evidenced by increased abstinence, reduction of craving, and control of withdrawal signs and symptoms – and a favorable safety profile for patients with OUD. In considering the risks in the context of the meaningful benefits that RBP-6000 would provide both to patients and public health, RBP-6000 has a favorable benefit risk profile for its intended use.

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10 APPENDICES

10.1 Inclusion and Exclusion Criteria for the Ph3DB Study

Inclusion Criteria:

Each subject was required to meet all of the following criteria to be randomized into the study.

1. Subject currently met DSM-5 criteria for moderate or severe opioid use disorder.
2. 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.
3. Subject was seeking MAT for opioid use disorder.
4. Subject was an appropriate candidate for opioid partial-agonist MAT in the opinion of the investigator or medically responsible physician.
5. Subject sex was male or female.
6. Subject age was ≥ 18 to ≤ 65 years.
7. Subject had BMI of ≥ 18.0 to ≤ 35.0 kg/m^2.
8. 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 enrolment, and agreed to use a medically acceptable means of contraception 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.

   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.
9. Subject agreed not to take any buprenorphine products other than those administered during the current study throughout participation in the study.
10. Subject was willing to adhere to study procedures and provide written informed consent prior to the start of any study procedures.

Exclusion Criteria:

Individuals who met any of the following criteria were to be excluded from the study.

1. Subject had a current diagnosis, other than opioid use disorder, requiring chronic opioid treatment.

2. 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.
3. 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.
4. Subject met DSM-5 criteria for moderate or severe alcohol use disorder.
5. Subject received MAT for opioid use disorder (e.g., methadone, buprenorphine) in the 90 days prior to providing written informed consent.
6. Subject's treatment for opioid use disorder was required by court order.
7. Subject's current incarceration or pending incarceration/legal action that could have prohibited participation or compliance in the study.
8. Subject was a pregnant or lactating female.
9. 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. More examples were provided in the excluded medications list.
10. 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.
11. 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.
12. Subject had clinically significant abnormal systolic blood pressure (BP) or diastolic BP, in the opinion of the investigator.
13. 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.
14. 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.
15. Subject had history or presence of allergic or adverse response (including rash or anaphylaxis) to buprenorphine, naloxone or the ATRIGEL Delivery System.

16. Subject had participated in any other clinical trial within 30 days prior to informed consent.
17. Subject had total bilirubin ≥ 1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) ≥ 3 × ULN, aspartate aminotransferase (AST) ≥ 3 × ULN, serum creatinine > 2 × ULN, international normalized ratio > 1.5 × ULN, lipase > 3 × ULN, amylase > 3 × ULN or any abnormal pancreatic enzyme value above ULN that was associated with a clinically significant, active pancreatic disorder.
18. 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.
19. 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.
20. Subject had diagnosis of acquired immunodeficiency syndrome.
21. Subject had previously received RBP-6000.
22. Subject was affiliated with, or a family member of, site staff directly involved in the study.
23. Subject was unable, in the opinion of the investigator or the medically responsible physician, to comply fully with the study requirements.
24. 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.

Beginning on the 7th day of SUBOXONE sublingual film dosing (Study Day -8) through the 14th day of dosing, subjects were evaluated for Day -1 criteria, which were identical to the criteria required for randomization on Day 1. Subjects must have met the following criteria in order to be randomized:

1. No allergic reaction to SUBOXONE sublingual film.
2. Daily dose of SUBOXONE sublingual film between 8 mg/2 mg - 24 mg/6 mg (inclusive) buprenorphine/naloxone.
3. COWS score of ≤ 12.
4. Opioid Craving VAS score of ≤ 20 mm.

10.2 Subject Disposition in the Phase 3 Studies

Table 32: Phase 3 Individual and Pooled Studies: Subject Disposition

Number of Subjects	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)	RBP-6000 300/300 (N = 201)	Placebo (N = 100)	RBP-6000 300 → 300/Flex (N=113)	RBP-6000 100 → 300/Flex (N=112)	PBO → RBP-6000 300/Flex (N=32)	RBP-6000 300/Flex (N=412)	Total RBP-6000 (N=848)
Completed [b]	125 (61.6)	129 (64.2)	34 (34.0)	47 (41.6)	61 (54.5)	14 (43.8)	2 (0.5)	153 (18.0)
Discontinued	78 (38.4)	72 (35.8)	66 (66.0)	28 (24.8)	15 (13.4)	5 (15.6)	164 (39.8)	362 (42.7)
Ongoing	NA	NA	NA	38 (33.6)	36 (32.1)	13 (40.6)	246 (59.7)	333 (39.3)
Reason for Discontinuation								
Lost to Follow-up	26 (12.8)	23 (11.4)	12 (12.0)	6 (5.3)	6 (5.4)	2 (6.3)	58 (14.1)	121 (14.3)
Withdrew Consent to Participate	20 (9.9)	21 (10.4)	18 (18.0)	14 (12.4)	7 (6.3)	2 (6.3)	53 (12.9)	117 (13.8)
Other	17 (8.4)	6 (3.0)	7 (7.0)	5 (4.4)	0	0	27 (6.6)	55 (6.5)
Adverse Events	6 (3.0)	10 (5.0) [a]	2 (2.0)	2 (1.8)	0	1 (3.1)	9 (2.2)	28 (3.3)
Protocol Violation	2 (1.0)	5 (2.5)	0	1 (0.9)	2 (1.8)	0	3 (0.7)	13 (1.5)
Lack of Efficacy	3 (1.5)	5 (2.5)	18 (18.0)	0	0	0	0	8 (0.9)
Withdrawn from Participation by the Investigator	1 (0.5)	0	3 (3.0)	0	0	0	6 (1.5)	7 (0.8)
Physician Decision	0	1 (0.5)	1 (1.0)	0	0	0	4 (1.0)	5 (0.6)
Withdrawal Symptoms	1 (0.5)	1 (0.5)	3 (3.0)	0	0	0	3 (0.7)	5 (0.6)
Noncompliance with Study Treatment	2 (1.0)	0	2 (2.0)	0	0	0	1 (0.2)	3 (0.4)
Study Terminated by Sponsor	0	0	0	0	0	0	0	0
Death	0	0 [a]	0	0	0	0	0	0

a. 1 subject in group RBP-6000 300/300 in Study 13-0001 discontinued due to AE that led to death (gun shot wound).
b. A subject was deemed to have completed the study if he/she had received 6 doses (roll-over) or 12 doses (de-novo) of RBP-6000 and completed the End of Study visit.

10.3 TEAEs Reported in Prescribing Information for SUBOXONE

Table 33: Adverse Events (≥5%) by Body System and Treatment Group in a 16-Week Study

Body System/ Adverse Event (COSTART Terminology)	Buprenorphine Dose (Sublingual Solution)				
	Very Low*N=184 n (%)	Low* N=180 n (%)	Moderate* N=186 n (%)	High* N=181 n (%)	Total* N=731 n (%)
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					
Cough increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin and Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

Table abstracted from SUBOXONE SL Film Prescribing Information

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:

1 mg solution would be less than a tablet dose of 2 mg
4 mg solution approximates a 6 mg tablet dose
8 mg solution approximates a 12 mg tablet dose
16 mg solution approximates a 24 mg tablet dose

Table 34: Adverse Events (≥ 5%) by System Organ Class and Treatment Group in a 4-Week Study

Preferred Term (MedDRA)	SUBOXONE Sublingual Tablets 16 mg/4 mg /day N=107 n (%)	SUBUTEX Sublingual Tablet 16 mg/day N=103 n (%)	Placebo N=107 n (%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Drug withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Hyperhidrosis	15 (14.0%)	13 (12.6%)	11 (10.3%)
Abdominal pain	12 (11.2%)	12 (11.7%)	7 (6.5%)
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Back pain	4 (3.7%)	8 (7.8%)	12 (11.2%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)

Table abstracted from SUBOXONE SL Film Prescribing Information

10.4 Narrative for Death in the Phase 3 Double-Blind Study

A 39-year-old male subject received a total of 2 injections of RBP-6000 containing 300-mg buprenorphine SC on 29 September 2015 and 29 October 2015. On (b) (6) the subject was found deceased from a gunshot wound. The subject's relatives declined to provide his medical records, death certificate or postmortem reports. Police declared that this was a case of homicide. The causality assessment by the investigator (reported causality) and sponsor (determined causality) for the event of gunshot wound was considered not related to study treatment.

10.5 eDISH Plots for Ph3DB and Ph3OL Studies

Figure 27: eDISH Plots of Peak Total Bilirubin (×ULN) and Peak ALT (×ULN) in Ph3DB Study

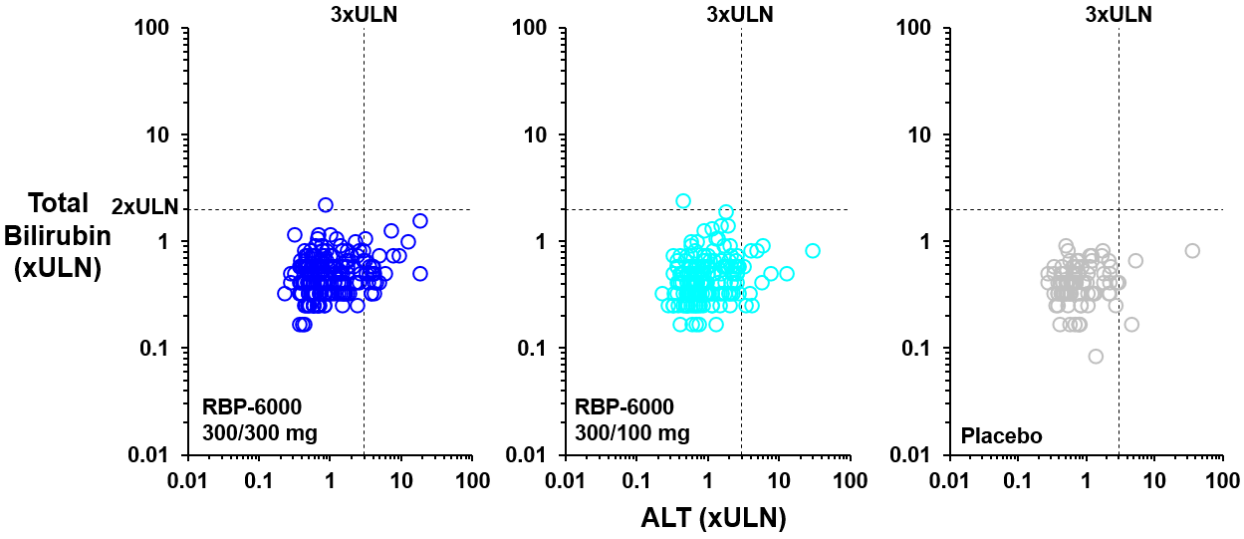

Figure 28: eDISH Plots of Peak Total Bilirubin (×ULN) and Peak AST (×ULN) in Ph3DB Study

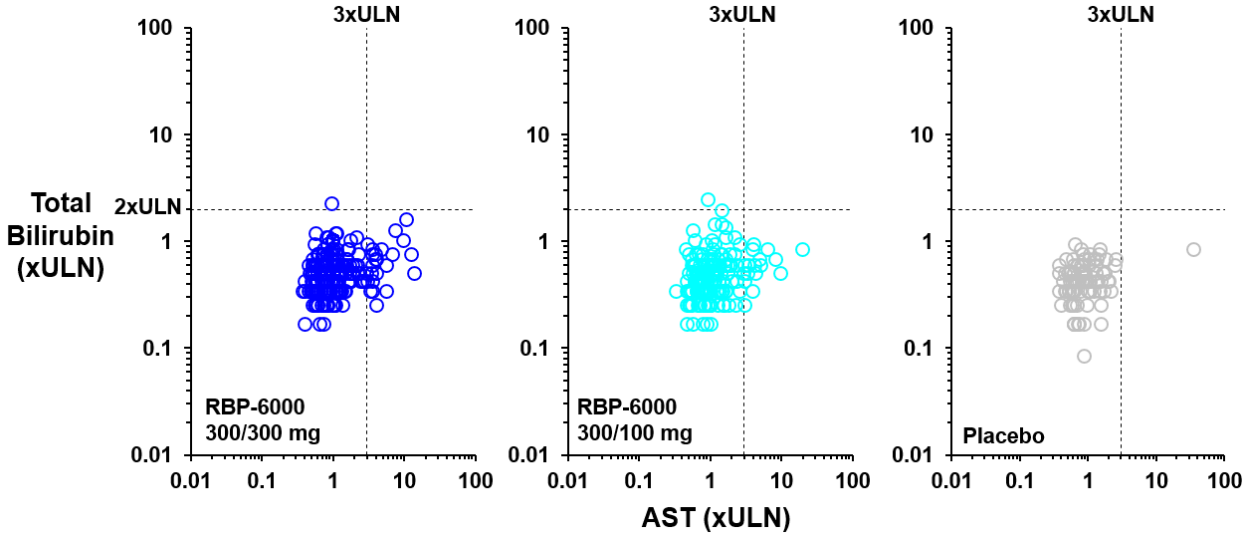

Figure 29: eDISH Plots of Peak Total Bilirubin (×ULN) and Peak ALT (×ULN) in Ph3OL Study

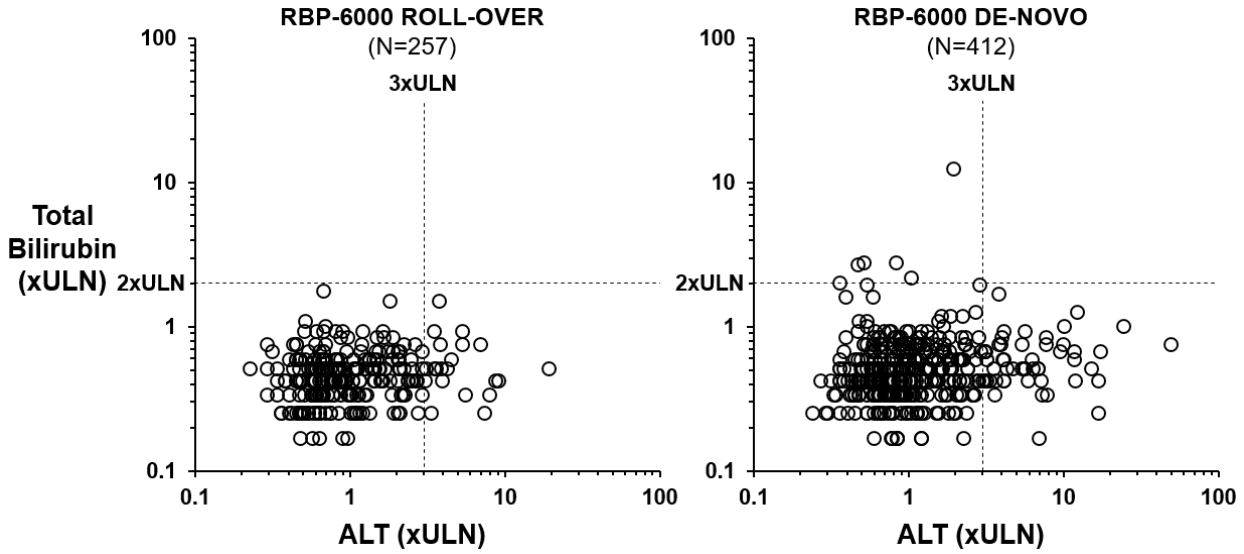

Figure 30: eDISH Plots of Peak Total Bilirubin (×ULN) and Peak AST (×ULN) in Ph3OL Study