

**Study Title**      An Open-Label, Long-Term Safety and Tolerability Study of Depot Buprenorphine (RBP-6000) in Treatment-Seeking Subjects With Opioid Use Disorder

**NCT Number**      NCT02510014

**Date**      August 4, 2016

## Clinical Study Protocol: RB-US-13-0003

**Study Title:** An Open-Label, Long-Term Safety and Tolerability Study of Depot Buprenorphine (RBP-6000) in Treatment-Seeking Subjects With Opioid Use Disorder

**Study Number:** RB-US-13-0003

**Study Phase:** 3

**Product Name:** RBP-6000

**IND Number:** 107,607

**Indication:** Treatment of Opioid Use Disorder

**Investigators:** Multicenter

**Sponsor:** Indivior Inc.

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	Date
<b>Original Protocol:</b>	14 April 2015
<b>Amendment 1:</b>	19 August 2015
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<b>Amendment 4:</b>	04 August 2016

### Confidentiality Statement

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## SYNOPSIS

<b>Sponsor:</b> Indivior Inc., formerly Reckitt Benckiser Pharmaceuticals Inc. (RBP)
<b>Name of Finished Product:</b> RBP-6000, 18% buprenorphine sterile solution for subcutaneous (SC) injection
<b>Name of Active Ingredient:</b> Buprenorphine
<b>Name of Inactive Ingredient:</b> ATRIGEL® Delivery System
<b>Study Title:</b> An Open-Label, Long-Term Safety and Tolerability Study of Depot Buprenorphine (RBP-6000) in Treatment-Seeking Subjects With Opioid Use Disorder
<b>Study Number:</b> RB-US-13-0003
<b>Study Phase:</b> Phase 3
<b>Primary Objective:</b> To assess the long-term safety and tolerability of RBP-6000 subcutaneous (SC) injections in subjects with opioid use disorder.
<b>Secondary Objective:</b> To collect clinical outcome data with RBP-6000 SC injections in subjects with opioid use disorder.
<b>Tertiary Objectives:</b> To evaluate the: <ul style="list-style-type: none"><li>• Pharmacokinetics (PK) of RBP-6000,</li><li>• Relationships between RBP-6000 PK and clinical outcome data, and</li><li>• Impact of RBP-6000 on health and economic outcomes.</li></ul>
<b>Study Design:</b> This is a multicenter, open-label, long-term safety study in which approximately 600 subjects diagnosed with opioid use disorder will be enrolled (approximately 300 subjects who did not participate in Study RB-US-13-0001, the double-blind, placebo-controlled efficacy study of RBP-6000 [hereafter referred to as “ <i>de novo</i> ” subjects], and 300 subjects who completed the RB-US-13-0001 study [hereafter referred to as “roll-over” subjects]). Subject participation will be based on the Investigator’s determination that initiation or continuation of study treatment is appropriate; and, for subjects who participated in RB-US-13-0001, that there have been no significant protocol deviations or clinically relevant adverse events (AEs) that would preclude inclusion of the subject in this study. All subjects will provide written informed consent before any protocol-related procedures commence. At the Screening Visit (which is up to 3 days after the End of Study [EOS] Visit [Day 169 + 3] for roll-over subjects), potential subjects will be

reviewed for eligibility against inclusion and exclusion criteria, and eligible subjects will be enrolled into the trial.

**SUBOXONE Sublingual Film Run-In: Induction**

***De novo* Subjects:**

*De novo* subjects will initially be inducted onto SUBOXONE® (buprenorphine/naloxone) sublingual film for 3 days according to the SUBOXONE sublingual film prescribing information. They will receive their first dose of SUBOXONE sublingual film on Induction Day 1 after it is confirmed that the subject meets eligibility criteria and has a Clinical Opiate Withdrawal Scale (COWS) score > 12. Subjects will be started with an initial dose of 2 mg/0.5 mg (buprenorphine/naloxone) or 4 mg/1 mg and may titrate upwards in 2 or 4 mg increments of buprenorphine, at approximately 2-hour intervals, under clinical supervision, to 8 mg/2 mg based on therapeutic response.

On Induction Day 2, subjects with a COWS score > 12 or subjects reporting withdrawal signs/symptoms overnight will receive a dose of SUBOXONE sublingual film equal to the total dose given on Induction Day 1 plus 4 mg. (For example, if a subject received a total dose of 8 mg of buprenorphine on Induction Day 1, the starting dose for Induction Day 2 would be 12 mg). If the COWS score is still > 12 one hour later, another 4 mg dose can be given. The subject should not exceed a maximum dose of 16 mg buprenorphine for Induction Day 2. Subsequent SUBOXONE sublingual film doses must be separated by at least 1 hour from the preceding dose. SUBOXONE sublingual film doses may also be adjusted downward if necessary.

On Induction Day 3, subjects will be titrated to therapeutic response based on COWS scores as well as physician judgment. Most subjects will only require a single dose on Induction Day 3, which will equal the Induction Day 2 dose or the Induction Day 2 dose plus 4 mg buprenorphine. Additional doses may also be administered on Induction Day 3 (up to 24 mg/6 mg). Subsequent SUBOXONE sublingual film doses must be separated by at least 1 hour from the preceding dose. Subjects should reach a daily dose of between 8 mg and 24 mg buprenorphine by Induction Day 3 and continue on that dose through the remainder of the SUBOXONE sublingual film Run-In period, with additional dose adjustments if necessary.

**Roll-over Subjects:**

Following screening, roll-over subjects will be inducted onto SUBOXONE sublingual film to achieve daily doses between 8 mg to 24 mg buprenorphine according to the SUBOXONE sublingual film prescribing information.

Subjects will receive their first induction dose on Induction Day 1. Subjects should be started with an initial dose of 2 mg/0.5 mg (buprenorphine/naloxone) or 4 mg/1 mg and may titrate upwards in 2 or 4 mg increments of buprenorphine, at approximately 2-hour intervals, under supervision, to a total dose of up to 8 mg/2 mg based on the control of acute withdrawal symptoms.

On Induction Day 2, subjects with a score for COWS of >12, or subjects reporting opioid withdrawal signs/symptoms overnight, should receive a dose of study drug equal to the total dose given on Induction Day 1 plus 4 mg. If the COWS score is still >12 one hour later, another 4 mg dose can be given. The subject should not exceed a maximum dose of 16 mg/4 mg for Induction Day 2. Subsequent SUBOXONE sublingual film doses must be separated by at least 1 hour from the preceding dose. SUBOXONE sublingual film doses may also be adjusted downward if

necessary.

On Induction Day 3, subjects will be titrated to therapeutic response until a therapeutic dosage is reached, based on COWS scores as well as physician judgment. Most subjects will only require a single dose on Induction Day 3 which will equal the Induction Day 2 dose or the Induction Day 2 dose plus 4 mg. Additional doses may also be administered on Induction Day 3 (up to 24 mg). Subsequent SUBOXONE sublingual film doses must be separated by at least 1 hour from the preceding dose. Although subjects should reach a daily dose of between 8 mg and 24 mg by Induction Day 3 and continue on that dose through the remainder of the SUBOXONE sublingual film Run-In period, dose adjustments may be necessary during the Run-In period.

Roll-over subjects must be titrated to a **minimum dose of 8 mg** SUBOXONE by the end of the 3-day Induction period regardless of their COWS scores and/or the presence or absence of withdrawal symptoms.

The SUBOXONE sublingual film(s) will be administered under the tongue, close to the base on the left or right side, until they are dissolved. If an additional sublingual film is required, it should be placed on the opposite side from the first film. Subjects should be instructed to hold the films under the tongue until they dissolve. If a third film is required, it should be placed under the tongue after the first 2 films have dissolved.

**SUBOXONE Sublingual Film Run-In: Dose Adjustment (All Subjects)**

After the daily induction visits, all subjects will begin a 1-to 11-day SUBOXONE sublingual film dose adjustment period. Subjects will return to the clinic at 3- to 4-day intervals for Opioid Craving Visual Analog Scale (VAS), COWS, and Subjective Opiate Withdrawal Scale (SOWS) assessments. SUBOXONE sublingual film will be dispensed at each visit for at home dosing. Beginning on the 4<sup>th</sup> day of SUBOXONE sublingual film dosing, subjects will be evaluated for Day -1 criteria, which are identical to the criteria required for enrollment on Day 1. These criteria include the following: no allergic reaction to SUBOXONE sublingual film, a daily dose of SUBOXONE sublingual film between 8 mg and 24 mg (inclusive) buprenorphine, a COWS score of  $\leq 12$ , and an Opioid Craving VAS score of  $\leq 20$  mm.

**Open-Label Treatment with RBP-6000:**

On Day 1 of the study (first dose of RBP-6000), all subjects who meet enrollment criteria will receive a SC injection of 300 mg of buprenorphine in RBP-6000. Subsequent doses of RBP-6000 may be adjusted down to 100 mg and back up to 300 mg based on the medical judgment of the Investigator. After injection of RBP-6000, subjects will not be permitted to receive supplemental SUBOXONE sublingual film during the RBP-6000 treatment period. Subjects who require supplemental SUBOXONE sublingual film or other sublingual buprenorphine pharmacotherapy during the RBP-6000 treatment period will be withdrawn from the study and referred for appropriate treatment.

Subjects will return to the clinic for monthly injection visits (every 28 - 2/+ 4 days) for a total of up to 12 injections for *de novo* subjects or for a total of 6 injections for roll-over subjects. Electrocardiogram (ECG) recordings and vital signs will be collected pre and post each SC injection. Subject-reported injection site pain Visual Analog Scale scores (VAS) will be collected at various times for 1 hour after each injection. Local injection site grading will be collected at various time points starting immediately after injection; the injection site will be evaluated for pain, tenderness, warmth, itching, erythema, inflammation or swelling, and

bruising using a 4-point severity scale. At each visit after injections begin, the injection site will be assessed by site staff for potential reaction and will also be evaluated for evidence of attempts to remove the depot.

Subjects will return to the clinic weekly for the first 5 weeks and then biweekly (i.e., every 2 weeks) through to injection 6. After injection 6, visits will be monthly for the rest of the study period for urine drug screens (UDS), Timeline Followback (TLFB) interviews, opioid craving VAS evaluation, COWS and subject reported outcomes (Subjective Opiate Withdrawal Scale [SOWS]). Subjects will continue to receive counseling (manual-guided behavioral therapy) during the study.

Safety assessments will be collected at each injection visit and/or at injection follow-up visits and will include the following: vital signs, electronic Columbia Suicide Severity Rating Scale (eC-SSRS) responses, ECGs, laboratory tests (hematology, chemistry, urinalysis, and pregnancy test), use of concomitant medications, and the frequency of AEs.

Sparse PK blood samples will be collected for population PK analysis from the roll-over subjects only. Once at least 75 roll-over subjects have completed Injection 6 (Week 25, Day 169) the sites will be notified that no more PK samples will be required to be collected from the roll-over subjects for the duration of the study. PK samples for population PK analysis are not required from the *de novo* subjects. ECGs will be performed before PK sample collection. The following health economic and outcome assessments will also be collected: Beck Depression Inventory (BDI-II), brief pain inventory (BPI), EuroQol EQ-5D-5L (EQ-5D-5L), 36-Item Short Form Health Survey, Version 2 (SF-36v2), Medication Satisfaction Questionnaire (MSQ), healthcare resource utilization (HCRU), Treatment Effectiveness Assessment (TEA), and Addiction Severity Index Lite (ASI).

For all subjects (*de novo* and roll-over), a PK sample will be taken as soon as possible after any SAE is reported. If possible, an additional sample should be collected when the SAE has been resolved.

Approximately 2 months prior to the scheduled End Of Study (EOS) visit, the subject's ongoing treatment options will be reviewed with the investigator. At the EOS, 2 transition treatment options may be offered if the subject is eligible:

- Subjects who complete the RBP-6000 treatment period may be offered entry into an open label extension study of RBP-6000 (Study INDV-6000-301). Eligibility will be based on meeting the inclusion and exclusion criteria and the medical judgment of the Investigator.
- Subjects who do not meet the eligibility criteria of the extension study, or subjects who do not wish to enroll may alternatively enter a 4-week SUBOXONE transition period if deemed suitable by the investigator. Subjects should be dosed using the Investigators medical judgement. Any additional unscheduled visits required by the subject for the SUBOXONE transition will not be compensated by the Sponsor.

Subjects that have not enrolled onto the INDV-6000-301 should be contacted by telephone approximately 4 weeks after EOS for a safety follow-up assessment of AEs and use of concomitant medications.

<b>Study Population:</b> Approximately 300 <i>de novo</i> subjects will be enrolled into this study, as well as approximately 300 roll-over subjects. The study population will consist of individuals diagnosed with opioid use disorder who are seeking treatment.
<b>Test Product, Dose, and Mode of Administration:</b> 300 mg buprenorphine in RBP-6000, subcutaneous injection 100 mg buprenorphine in RBP-6000, subcutaneous injection
<b>Duration of Study Treatment:</b> This will be a multiple-dose study, with the first investigational product administration (RBP-6000 containing 300 mg buprenorphine) on Day 1. The expected maximum duration of participation for <i>de novo</i> subjects is up to approximately 55 weeks, consisting of up to 7 days of screening, up to 14 days SUBOXONE sublingual film Run-In, up to a 48-week open-label treatment period, and a 4-week safety follow-up telephone call. The expected maximum duration of participation for roll-over subjects is up to approximately 31 weeks, consisting of up to a 7-day screening period, up to 14 days SUBOXONE sublingual film Run-In, a 24-week open-label treatment period, and a 4-week safety follow-up telephone call. Subjects who enroll in the INDV-6000-301 study are not required to complete the safety follow-up telephone call.
<b>Safety Assessments:</b> Safety objectives for this study are to evaluate the safety and tolerability of RBP-6000 (100 mg and 300 mg) SC injection treatment in subjects with opioid use disorder. Safety assessments will include the following: frequency of all AEs, serious AEs (SAEs), discontinuations from study due to AEs; local injection site tolerability (e.g., injection site grading); injection site pain using a subject-reported VAS; suicidality using the eC-SSRS, use of concomitant medications; changes in clinical laboratory results; vital sign measurements; 12-lead ECGs, which will be interpreted by a central facility; physical examination results; body weight, height, and body mass index (BMI), and abdominal fat measurement (waist-to-hip ratio).
<b>Clinical Outcome Assessments:</b> Clinical outcome assessments will include the UDS for opioids and other drugs; self-reported use of illicit opioids, other drugs, and alcohol on the TLFB; COWS, SOWS, and Opioid Craving VAS.
<b>PK Assessments:</b> Sparse plasma samples will be collected for population PK analysis from the roll-over subjects only. Once at least 75 roll-over subjects have completed Injection 6 (Week 25 Day 169), the sites will be notified that no more PK samples will be required to be collected from the roll-over subjects for the duration of the study. No PK samples will be collected from the <i>de novo</i> subjects. However, for all subjects ( <i>de novo</i> and roll-over) throughout the study, a PK sample will be taken as soon as possible after any SAE is reported. If possible, an additional sample should be

collected when the SAE has been resolved.

**Health Economics and Outcomes Assessments:**

Health economics and outcomes assessments will include: BDI-II, BPI, EQ-5D-5L, SF-36v2, MSQ, HCRU, TEA, and ASI-Lite.



**Statistical Methods:**

A Statistical Analysis Plan (SAP) will be prepared after the protocol is approved and before database lock occurs. The SAP will provide further details regarding the definition of analysis endpoints, data handling rules, and the statistical methodology to be used to address all study objectives. The SAP will also include formats for the summary and analysis tables, listings, and graphical displays.

**Determination of Sample Size:**

Approximately 300 *de novo* subjects as well as approximately 300 subjects who completed the RB-US-13-0001 study will be enrolled into this long-term safety study to ensure 100 subjects reach 1 year of treatment with RBP-6000. No power analysis will be done corresponding to the sample sizes, but the large numbers proposed are clinically acceptable to provide adequate and relevant clinical conclusions from this study.

**Safety Analyses:**

Safety variables will include AEs, local injection site tolerability (e.g., injection site grading); injection site pain using a subject-reported VAS; suicidality using the eC-SSRS, concomitant medications; changes in clinical laboratory results (hematology, chemistry and urinalysis); vital sign measurements; 12-lead ECGs, physical examination results; body weight, height, BMI, and abdominal fat measurement (waist-to-hip ratio). Safety variables will be analyzed on the safety population using descriptive statistics for continuous endpoints (e.g., mean, median, SD, minimum and maximum) and frequency counts with percentages for discrete endpoints.

Baseline is defined as the last non-missing value prior to SC injection on Day 1. No imputation of missing values will be performed.

**Clinical Outcomes Assessments:**

COWS, SOWS and Opioid Craving VAS total scores will be summarized using descriptive statistics (mean, median, SD, minimum, maximum), including change from baseline. Subjects' self-reported illicit drug use from the TLFB will be summarized as descriptive statistics.

The cumulative distribution function (CDF) of the percentage of urine samples negative for opioids, the CDF of the percentage of self-reports from the TLFB negative for illicit opioid use, and other outcome measures will be calculated.

**Population PK/PD Analysis:**

The population PK model established using the data collected in the double-blind, placebo-controlled, efficacy study (Study RB-US-13-0001) will be refined using the PK samples collected in the present study to characterize the disposition of buprenorphine and norbuprenorphine following SC injections of RBP-6000, with the assessment of potential covariates affecting the PK of both compounds. Subsequently, the relationships between buprenorphine plasma concentrations and clinical outcomes assessments will be investigated. These relationships will be initially assessed in a descriptive manner, and, if applicable, appropriate PK/PD models will be developed to describe these relationships. A stand-alone modeling analysis plan will be generated, and the results will be reported in a standalone modeling report.

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**Health Economic and Outcomes Research Analyses:**

The health economic and outcomes research endpoints for this study are: BDI-II, BPI, EQ-5D-5L, SF-36v2, MSQ, Health Insurance, HCRU, TEA, and ASI-Lite.

Summary scores for these measures will be calculated, as appropriate. Categorical variables will be summarized using frequencies and percentages. Continuous measures will be summarized using descriptive statistics (mean, standard deviation, median, minimum, maximum) as appropriate. An analysis of change will be conducted. Supplementary analyses using general linear, mixed, or non-parametric methods will be performed as appropriate.

A stand-alone SAP will be developed prior to database lock with full detail regarding health economics and outcomes analyses.

**Date of Original Approved Protocol:** 14 April 2015

**Date of Amendment 1:** 19 August 2015

**Date of Amendment 2:** 11 September 2015

**Date of Amendment 3:** 25 March 2016

**Date of Amendment 4:** 04 August 2016

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## LIST OF ABBREVIATIONS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ANOVA	analysis of variance
ASI-Lite	Addiction Severity Index - Lite
AUC	area under the plasma concentration-time curve
BDI-II	Beck Depression Inventory - II
BMI	body mass index
BP	blood pressure
BPI	Brief Pain Inventory Short Form
$C_{avg}$	average plasma concentration
$C_{max}$	maximum plasma concentration
$C_{trough}$	plasma concentration at trough, i.e. before the next injection
CDF	cumulative distribution function
CNS	central nervous system
COWS	Clinical Opiate Withdrawal Scale
CRA	clinical research associate
DAWN	Drug Abuse Warning Network
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 <sup>th</sup> Edition
EC <sub>50</sub>	concentration yielding 50% of the maximal effect
eCRF	electronic case report form
e C-SSRS	Electronic Columbia Suicide Severity Rating Scale
$E_{max}$	maximum effect
ECG	electrocardiogram
ED	emergency department
EOS	end of study
ET	early termination
EQ-5D	EuroQol EQ-5D (standard instrument)
EQ-5D-5L	EuroQol EQ-5D-5L (self-complete version)

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EQ-VAS	EQ-5D using visual analog scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
hCG	urine human chorionic gonadotropin
HCl	hydrochloride
HCRU	healthcare resource utilization
HEOR	health economics and outcomes research
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IM	intramuscular
IMP	investigational medicinal product
IND	investigational new drug application (i.e., Notice of Claimed Investigational Exemption for a New Drug)
INDV	Indivior Inc.
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
IWRS	interactive web response system
MAR	missing at random
MCAR	missing completely at random
MMRM	mixed model repeated measures
MSQ	Medication Satisfaction Questionnaire
NMP	N-methyl pyrrolidone
NOAEL	no observable adverse effect level
OTC	over-the-counter

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PD	pharmacodynamic or pharmacodynamics
PE	physical examination
PK	pharmacokinetic or pharmacokinetics
PLG or PLGH	poly (DL-lactide-co-glycolide)
PET	positron emission tomography
PI	Principal Investigator
PT	prothrombin time
PTT	partial thromboplastin time
RBP	Reckitt Benckiser Pharmaceuticals Inc.
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SF-36v2	36-Item Short Form Health Survey, Version 2
SL	sublingual
SOE	schedule of events
SOP	standard operating procedure
SOWS	Subjective Opiate Withdrawal Scale
$t_{\max}$	time to maximum plasma concentration
TEA	Treatment Effectiveness Assessment
TEAE	treatment-emergent adverse event
TLFB	timeline followback
UDS	urine drug screen
ULN	upper limit of normal
US/USA	United States/United States of America
VAS	visual analog scale

# 1 INTRODUCTION

## 1.1 Opioid Use Disorder

Opioid use disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association 2013), is a neurobehavioral syndrome characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and/or physical consequences. Opioid use disorder is a medical illness with high costs to individuals, families, and society. Direct and indirect costs attributable to illicit drug use are estimated in 3 principal areas: crime, productivity, and health (US Department of Justice, Economic Impact of Illicit Drug Use on American Society, 2011). Approximately one-third of all acquired immunodeficiency syndrome (AIDS) cases diagnosed in the United States (US) through 2009 (Centers for Disease Control and Prevention: HIV/AIDS Surveillance Report, 2009) and many cases of hepatitis C (National Institute on Drug Abuse 2000; Thomas 2001) were associated with injection drug use.

The increasing abuse of and addiction to prescription opioids is another major concern. According to the Substance Abuse and Mental Health Services Administration's Office of Applied Studies, the incidence of abuse of prescription opioid pain medications (narcotic analgesics) such as hydrocodone, oxycodone, meperidine, and propoxyphene has risen markedly in recent years (Crane 2003). The incidence of emergency department (ED) visits related to these medications has been increasing since the 1990s and has more than doubled between 1994 and 2001 (Crane 2003). The most recently published data from the Drug Abuse Warning Network (Drug Abuse Warning Network, 2009: National Estimates of Drug-Related Emergency Department Visits, 2011) estimated that about 2.1 million ED visits resulted from drug misuse or abuse, which was the equivalent of 674.4 ED visits per year per 100,000 population. Although the overall number of ED visits attributable to drug misuse or abuse was stable from 2004 to 2009, increases were seen in ED visits involving nonmedical use of pharmaceuticals with no other drug involvement (117% increase). An estimated 1,079,683 ED visits in 2009 involved the nonmedical use of prescription drugs, over-the-counter (OTC) medicines, or other types of pharmaceuticals, representing about a quarter of all drug-related ED visits and over half of ED visits for drug abuse or misuse. Pain relievers were the most common type of drugs reported in the nonmedical use category of ED visits (47.8%). Among specific types of pain relievers, narcotic pain relievers such as oxycodone, hydrocodone, and methadone (13.7%, 8.0%, and 5.8%, respectively) were most prevalent (Drug Abuse Warning Network, 2009: National Estimates of Drug-Related Emergency Department Visits, 2011).

The economic burden of prescription opioid abuse is very high. Total US societal costs of prescription opioid abuse were estimated at \$55.7 billion in 2007 (US dollars in 2009). Workplace costs accounted for \$25.6 billion (46%), health care costs accounted for \$25.0 billion (45%), and criminal justice costs accounted for \$5.1 billion (9%) (Birnbaum 2011). Mean annual direct health care costs for opioid abusers were more than 8 times higher than for nonabusers. Hospital inpatient and physician outpatient costs accounted for 46% and 31% respectively, of opioid abusers' health care costs. The high costs of opioid abuse are driven primarily by high comorbidity rates and high utilization rates of medical services and prescription drugs (White 2005). It was also found that opioid use results in lower quality of life,

including significantly worse physical and psychological health, compared with the general population (Ryan 1996).

Given the high costs of opioid addiction to individuals, families, and society, treatments for this disease therefore aim to reduce the use of prescription or illicit opioids as well as the risks associated with injection, including transmission of human immunodeficiency virus (HIV) and hepatitis C virus. Implantable formulations of opioid receptor partial agonists and antagonists represent an innovative alternative to daily dosing regimens, and several delivery systems are currently in clinical trials (Ling 2010, Rosenthal 2013). The goal of this study is to determine whether RBP-6000, which is a sustained release formulation of buprenorphine in the ATRIGEL<sup>®</sup> delivery system, is a safe and effective treatment for opioid use disorder.

## 1.2 Buprenorphine

In the central nervous system (CNS), opioid receptors are found in high concentrations in the limbic system and the spinal cord. The natural ligands for these receptors are a group of neuropeptides known as endorphins. Opioid analgesics mimic the action of endorphins but have a more prolonged action because the analgesics are not subject to rapid local metabolism.

Three major opioid receptor subclasses have been identified: mu, kappa, and delta. These subclasses mediate distinct actions with natural endorphins and opioid analgesics. Different endorphin and opioid analgesic ligands demonstrate different binding affinities for the various subclasses of receptors.

Buprenorphine is a member of the large family of opioid analgesics used in the treatment of moderate and severe acute and chronic pain. Opioid receptors are found in both the CNS and the periphery. Buprenorphine is a partial agonist at the mu receptor, producing a sub-maximal response compared to that of a full agonist. Hence, buprenorphine provides a greater margin of safety regarding respiratory depression in comparison to full agonist opioids. Buprenorphine is also an antagonist at the kappa receptor (Cowan 1977, Jasinski 1978).

Buprenorphine has been reported to have a lower physical dependence liability than pure agonist analgesics such as morphine, and at a sufficient dose, it can suppress opioid withdrawal signs and symptoms for at least 24 hours. Limited euphoric and respiratory depressant effects have led to its therapeutic use as a pharmacotherapy for opioid use disorder.

Selected pharmacokinetic (PK) parameters for buprenorphine when administered sublingually as buprenorphine/naloxone films are in the SUBOXONE sublingual film prescribing information ([Appendix 7](#)). Further details on the PK of buprenorphine in the ATRIGEL delivery system are described in Section [1.4.2](#).

## 1.3 ATRIGEL Delivery System

The ATRIGEL Delivery System is a sterile, polymeric solution of a biodegradable poly DL-lactide-co-glycolide (PLGH) copolymer, dissolved in the water-miscible, biocompatible solvent N-methyl pyrrolidone (NMP). The polymers belong to a family of poly  $\alpha$ -hydroxy acids that are used in medical devices such as resorbable sutures and degradable drug delivery

systems. Polymerization, which is initiated with glycolic acid, leads to a linear polymer containing a carboxylic acid end group. The ATRIGEL Delivery System can be formulated to deliver different active ingredients for various lengths of time.

The ATRIGEL Delivery System is well characterized. It is currently used in 7 approved products worldwide, including 4 ELIGARD<sup>®</sup> products (subcutaneous [SC] depot formulations of leuprolide acetate), ATRIDOX<sup>®</sup> (doxycycline hyclate applied to the periodontal pocket), the ATRISORB<sup>®</sup> Bioabsorbable Guided Tissue Regeneration Barrier for periodontal application, and the ATRISORB-D Barrier (ATRISORB with doxycycline) for periodontal guided tissue regeneration.

Clinical studies with these products demonstrated that the ATRIGEL Delivery System was well tolerated and provided consistent sustained release of the incorporated drug over the designated dosing interval. Injection site reactions are expected to be mild and appear early in treatment, as observed in previous local irritation ATRIGEL studies ([RBP-6000 Investigator's Brochure \[IB\] Edition 5, 18 May 2016](#)).

## **1.4 Buprenorphine in the ATRIGEL Delivery System (RBP-6000)**

RBP-6000 is a subcutaneously injected depot product under development for the treatment of opioid addiction. It contains buprenorphine in the ATRIGEL Delivery System and provides sustained plasma levels of buprenorphine over a minimum of 28 days. There is no currently approved, parenterally administered, sustained-release buprenorphine formulation for the treatment of opioid use disorder. Such a formulation could offer advantages over existing buprenorphine products by improving subject compliance and reducing diversion, abuse, and unintended exposure (e.g., in pediatric exposure), and reduce chances of swallowing drug.

The safety profile and clinical efficacy of RBP-6000 are expected to be similar to and comparable with that of buprenorphine or SUBOXONE sublingual treatment.

### **1.4.1 Summary of Nonclinical Data**

Nonclinical data suggest that toxicity from RBP-6000 is unlikely at the doses planned for this clinical study. The no observable adverse effect levels (NOAELs) were determined to be 250 mg/kg (rat) and 40 mg/kg (dog) following single SC injections of RBP-6000 in 4-week toxicity studies. These levels are equivalent to human buprenorphine doses of 2419 mg and 1333 mg, respectively (based on 60 kg body weight and calculated according US Food and Drug Administration guidance [FDA 2005]). These levels provide approximately 8.1x (rat) and 4.4x (dog) safety margins when compared to the 300-mg buprenorphine dose in humans (based on 60 kg body weight and calculated according US Food and Drug Administration guidance [FDA 2005]). Systemic effects seen in the rat and dog 4-week toxicity studies were related to the pharmacology of buprenorphine or local tolerance effects of the formulation as a result of high dose and volume, so the safety margins are considered acceptable.

Chronic repeated-dose studies were conducted in rats and dogs dosed with RBP-6000 once every 4 weeks for 6 or 9 months, respectively. These studies demonstrated systemic effects consistent with buprenorphine administration, such as stained fur, aggressive behavior, decreased activity,

reduced food consumption and body weight gain, and abnormal feces. Minimal to mild lung alveolar macrophage infiltration and pancreatic acinar cell apoptosis were seen with increased incidence in rats, but not dogs, treated with RBP-6000. Injection site findings were seen in both species, characterized microscopically by minimal to moderate granuloma formation. Injection volumes were high, being 2.73 mL/m<sup>2</sup> in rats and 3.64 mL/m<sup>2</sup> in dogs, compared with a volume of 0.62 mL/m<sup>2</sup> at the highest proposed clinical dose, contributing to these local findings. Systemic chronic NOAELs were considered to be 10 mg/kg in rats and 40 mg/kg in dogs.

Overall, the extensive preclinical data on both the buprenorphine and SUBOXONE products and nonclinical PK and toxicity studies in rats and dogs support the clinical development of RBP-6000. Systemic exposure to buprenorphine is not considered to pose any significant safety concerns following SC administration of RBP-6000. Additionally, this clinical study will be conducted in subjects who have a current diagnosis of opioid use disorder and who would thus be expected to have a certain degree of cross-tolerance to the opioid agonist effects of buprenorphine. Minimal to moderate irritation at the injection site, seen in both rats and dogs, may warrant attention to ensure local tolerability (RBP-6000 IB, Edition 4, 24 February 2014).

#### 1.4.2 Summary of Previous Clinical Data

In the first-in-human trial to evaluate the safety, tolerability, and PK of RBP-6000, 12 subjects received a single SC injection of RBP-6000 containing 20 mg of buprenorphine. Of these 12 subjects, 6 subjects completed the study through Day 85. The majority (94%) of treatment-emergent adverse events (TEAEs) were mild, 5.4% were moderate, and 1 was severe in intensity. TEAEs considered related to the study drug included injection site pain, injection site warmth, and injection site bruising, erythema, and edema. All subjects experienced mild to moderate symptoms of withdrawal at study entry, prior to study drug injection, and after study drug injection. One serious adverse event (SAE) was reported. The SAE was notably identified psychosocial stressors and intermittent withdrawal, for which the subject had prolonged hospitalization for treatment. This SAE was not considered to be related to the study drug. No respiratory depression, temperature elevations, clinically significant lowering of oxygen saturation, or electrocardiogram (ECG) abnormalities were observed. There was 1 clinically significant laboratory adverse event (AE; elevated hepatic enzymes), which resolved. No unexpected side effects occurred in the RBP-6000 depot formulation of buprenorphine (RBP-6000 IB, Edition 4, 24 February 2014). Buprenorphine was rapidly absorbed over the first day and peaked on the second day, with a slow decrease in plasma concentrations thereafter that is consistent with the slow release of buprenorphine from the ATRIGEL Delivery System.

The PK of 50, 100, and 200 mg buprenorphine (as RBP-6000) was also evaluated in a single-ascending-dose study in 51 subjects (RB-US-11-0020). In this study, median buprenorphine time to peak concentration ( $t_{max}$ ) in the initial burst period was observed at 24 hours for all 3 dosages. Buprenorphine mean plasma terminal half-life increased slightly with the increase in dose from 50 mg to 200 mg (1078 hours [44.9 days] at 50 mg, 1376 hours at 100 mg, and 1573 hours at 200 mg). Buprenorphine exhibited overall geometric mean average concentration values of 0.356, 0.624, and 1.108 ng/mL, respectively with 50, 100 and 200 mg buprenorphine while overall geometric mean  $C_{max}$  values of 0.999, 1.518, and 2.381 ng/mL were observed for buprenorphine doses of 50, 100, and 200 mg, respectively. With an increase in dose of RBP-

6000 from 50 to 200 mg, mean buprenorphine exposure parameters increased less than proportionally to dose (RBP-6000 IB, Edition 4, 24 February 2014). A single SC injection of RBP-6000 was generally safe and well tolerated. A total of 46 of 51 subjects (90.2%) had at least 1 TEAE. A total of 30 of 51 subjects (58.8%) had TEAEs that were related to treatment with RBP-6000. The majority of AEs were qualified as moderate in severity (68.6%). Two subjects reported TEAEs that were considered to be severe but unrelated to RBP-6000. No subjects withdrew from the study because of an AE.

The safety profile of multiple-dose SC injections of RBP-6000 containing 50 mg, 100 mg, 200 mg, and 300 mg of buprenorphine in treatment-seeking, opioid-dependent subjects in an open-label, multiple-dose study has recently been examined. The results suggest that all doses were safe and well-tolerated following a 13-day induction and stabilization on SUBUTEX. In addition, a study investigating the blockade of subjective opioid effects demonstrated that RBP-6000 was safe and well tolerated after the SC administration of 2 monthly 300-mg doses of buprenorphine in RBP-6000, following a 14-day induction and stabilization period on SUBOXONE Film.

#### 1.4.3 Pharmacokinetic/Pharmacodynamic Modeling of RBP-6000

A population PK model was developed to characterize the disposition of buprenorphine and norbuprenorphine following SC injection of RBP-6000 (Nasser 2014). This model was built using plasma concentration data collected in 36 opioid-dependent subjects who received single doses (50 mg, 100 mg, and 200 mg) of RBP-6000 in the single-ascending-dose study (RB-US-11-0020). Analysis of the PK profiles of RBP-6000 revealed a complex and multi-phase absorption profile, presenting double peaks and a prolonged plasma terminal half-life. These distinguishing features of the PK of RBP-6000 required the development of a complex structural PK model accounting for this dual absorption process: a first absorption process that was associated with an initial, rapid delivery from the SC injection site, and a second absorption process that was associated with the slow release of buprenorphine from the ATRIGEL Delivery System into the systemic circulation. The population PK model accurately predicted the PK data after repeated doses of RBP-6000 in the multiple ascending dose study (RB-US-12-0005) and in the opioid blockade study (RB-US-13-0002).

Another population PK/PD model was developed to characterize the link between buprenorphine plasma concentration and mu opioid receptor occupancy (Nasser 2014). Individual data from 15 heroin-dependent subjects were taken from two published clinical trials (Greenwald 2003; Greenwald 2007). A saturable maximum effect ( $E_{\max}$ ) model with 0.67 ng/mL effective concentration at 50% of maximum ( $EC_{50}$ ) and 91%  $E_{\max}$  best described mu opioid receptor occupancy versus buprenorphine plasma concentrations. At buprenorphine concentrations greater than 2 ng/mL, saturation occurred on mu opioid receptor occupancy where a 4.5-fold increase in observed buprenorphine concentrations resulted in observed mu opioid receptor occupancy between 70% and 90%.

Positron emission tomography (PET) scan data were obtained in 2 subjects participating in the multiple-ascending dose study RB-US-12-0005 (PET scan sub-study) and receiving either 200 or 300 mg of RBP-6000. The PET scans were conducted at 7 days and 28 days post-dose following



the 12<sup>th</sup> SC injection for the first subject receiving 200 mg, and following the 6<sup>th</sup> SC injection for the second subject receiving 300 mg. Both subjects were considered to be at steady-state for buprenorphine at the time of the PET scan measurements. The mu opioid receptor availabilities of four different regions in the brain were measured, and the mu opioid receptor occupancy in the whole brain was calculated as described in Greenwald et al. (2003).

The subject receiving 200 mg of RBP-6000 in the PET scan sub-study showed 79% and 75% mu opioid receptor occupancy on Day 7 and Day 28, respectively, following the 12<sup>th</sup> SC injection of RBP-6000. The subject receiving 300 mg of RBP-6000 in the PET scan sub-study showed 92% and 81% mu opioid receptor occupancy on Day 7 and Day 28, respectively, following the 6<sup>th</sup> SC injection of RBP-6000. These values and the corresponding PK concentrations were in agreement with the model predictions and the previous individual observations used to build the population PK/PD model.

Linear relationships were found between mu opioid receptor occupancy and opioid withdrawal symptoms, and between mu opioid receptor occupancy and hydromorphone agonist blockade, based on the data from 15 heroin-dependent subjects (Nasser 2014). These data suggest that a mean buprenorphine plasma concentration of 2 ng/mL is able to provide 70 % mu opioid receptor occupancy associated with low reported agonist drug effects and withdrawal symptoms (scores  $\leq 2$ ).

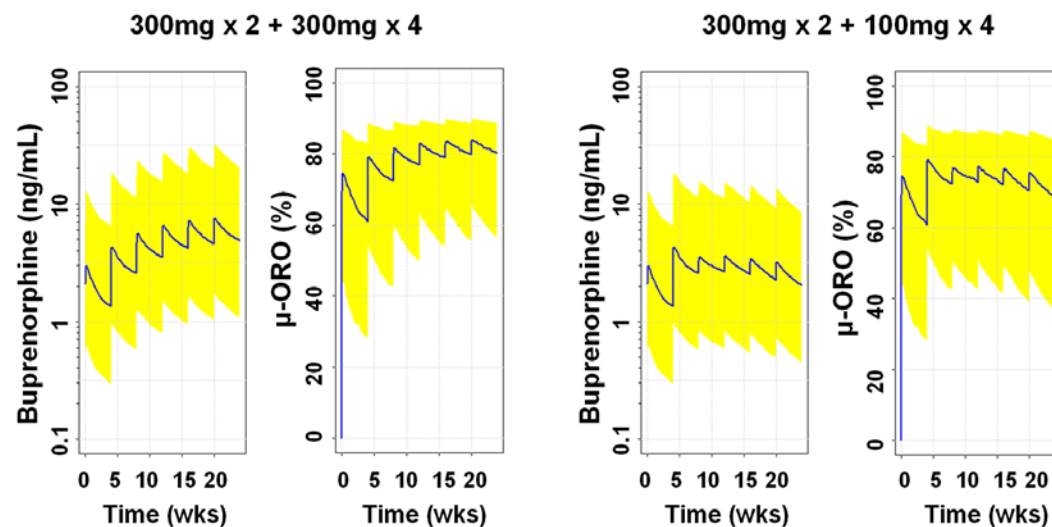
Model simulations indicated that the desired 70% mu opioid receptor occupancy may be achieved after multiple doses of 200 mg of RBP-6000 (Nasser 2014). The 300 mg dose was considered to be a full opioid blockade dose.

## 1.5 Rationale for Dose Selection

The results of the opioid blockade study (RB-US-13-0002) showed that 300 mg was a full opioid blocking dose (i.e., for the “drug liking” VAS scores the upper bound of the 95% confidence interval  $\leq 11$ ), which is consistent with PK/PD modeling and simulation results. The least means “drug liking” VAS scores in the opioid blockade study showed that the blockade was achieved from the first SC injection and was maintained after the second SC injection until week 12 (i.e., 2 months after the second injection).

The population PK and PK/PD models presented in Section 1.4.3 were used to simulate the double-blind efficacy study (RB-US-13-0001). The results of these simulations are displayed in Figure 1 for the two treatment arms on RBP-6000 receiving either 6 SC injections of 300 mg ( $300 \text{ mg} \times 2 + 300 \text{ mg} \times 4$ ), or 2 SC injections of 300 mg followed by 4 SC injections of 100 mg ( $300 \text{ mg} \times 2 + 100 \text{ mg} \times 4$ ).

**Figure 1**      **Model-Predicted Buprenorphine Plasma Concentrations and Mu-Opioid Receptor Occupancy in Each Treatment Group on RBP-6000 Following the Proposed Design of the Current Study**



The blue line represents the median model prediction; the yellow areas represent the 5<sup>th</sup> and the 95<sup>th</sup> percentiles of the predictions; μ-ORO: mu opioid receptor occupancy; wks: weeks.

The PK parameters calculated from the simulated typical PK profile of buprenorphine are listed in [Table 1](#). Average buprenorphine plasma concentration ( $C_{avg}$ ) over the monthly dosing interval was 1.9 ng/mL after the first SC injection at 300 mg, and 3.1 ng/mL after the second SC injection at 300 mg.

For the subjects receiving 6 monthly SC injections of RBP-6000 at 300 mg, the predicted  $C_{avg}$  value after the 4<sup>th</sup> SC injection was 5.1 ng/mL, which is close to mean value of 4.8 ng/mL observed in the multiple-ascending dose study. The predicted  $C_{avg}$  value after the 6<sup>th</sup> SC injection was 6.0 ng/mL. For the patients receiving 2 monthly SC injections at 300 mg followed by 4 monthly SC injections at 100 mg, the predicted  $C_{avg}$  after the 6<sup>th</sup> SC injection was 2.6 ng/mL. All these values were above the 2 ng/mL threshold for achieving the desired efficacy.

Overall, the modeling and simulation work and the opioid blockade study have shown that the 300 mg SC dose is an appropriate dose to assess for efficacy. The current study will therefore evaluate the long-term safety and tolerability of this dose. It is recognized, however, that some individuals may need lower doses based on genetic variations, abuse behavior, etc. Accordingly, subsequent doses of RBP-6000 may be adjusted down to 100 mg and back up to 300 mg based on the medical judgment of the Investigator.

**Table 1 PK Parameters of the Simulated Typical PK Profile of Buprenorphine after Repeated RBP-6000 Injections for the Phase 3 Efficacy Study (RB-US-13-0001)**

Buprenorphine (ng/mL)	SC Injection Number																
	1		2			3			4			5			6		
	C <sub>max</sub>	C <sub>avg</sub>	C <sub>max</sub>	C <sub>trough</sub>	C <sub>avg</sub>	C <sub>max</sub>	C <sub>trough</sub>	C <sub>avg</sub>	C <sub>max</sub>	C <sub>trough</sub>	C <sub>avg</sub>	C <sub>max</sub>	C <sub>trough</sub>	C <sub>avg</sub>	C <sub>max</sub>	C <sub>trough</sub>	C <sub>avg</sub>
<b>300mgx2 + 100mgx4</b>	2.9	1.9	4.2	1.3	3.1	3.5	2.5	3.0	3.6	2.6	3.0	3.5	2.5	2.8	3.2	2.3	2.6
<b>300mgx2 + 300mgx4</b>	2.9	1.9	4.2	1.3	3.1	5.4	2.5	4.3	6.4	3.5	5.1	7.1	4.2	5.7	7.5	4.6	6.0

C<sub>max</sub>: maximum plasma concentration; C<sub>avg</sub>: average plasma concentration; C<sub>trough</sub>: plasma concentration at trough (ie, before the next injection).

## 1.6 Known and Potential Risks and Benefits

The AE profile of buprenorphine is well-characterized; commonly reported effects include constipation, nausea, vomiting, and headache. Buprenorphine is approved for use by various routes of administration (e.g., SL, intramuscular [IM], intravenous [IV], transdermal, and rectal).

Studies of buprenorphine receptor binding in human subjects have consistently and reproducibly established that buprenorphine is a highly lipophilic, mu-opioid receptor partial agonist with slow receptor association and dissociation kinetics. Buprenorphine has an improved safety profile relative to mu-opioid receptor full agonists due to its partial agonist properties. These attributes of buprenorphine allow it to perform well as substitution therapy for opioid-dependent individuals over short-term and long-term durations. The experiments used to establish the binding profile of buprenorphine were consistent across differing parenteral routes of administration (IV, IM, and SL); therefore, RBP-6000 is expected to perform similarly when administered as a SC depot in the ATRIGEL Delivery System.

The efficacy of buprenorphine in the treatment of opioid dependence has been well established (see for example, New Drug Applications 20-732; 20-733; 22-410). Buprenorphine has been used for medically-supervised taper (i.e., detoxification) medication and as a long-term medication assisted therapy (i.e., maintenance). A recent Cochrane Review meta-analysis revealed that buprenorphine is statistically significantly superior to placebo in the retention of subjects and reduction of opioid-positive urine tests, and that buprenorphine and methadone may be equally efficacious at adequate dose levels of both medications (Mattick 2008).

A sustained-release formulation of buprenorphine using the ATRIGEL Delivery System offers a number of potential benefits relative to shorter-acting formulations, including improved subject compliance, reduced diversion and misuse, as well as a reduced risk to subjects, their families, and the community.

## **2 STUDY OBJECTIVES**

Indivior Inc., formerly Reckitt Benckiser Pharmaceuticals Inc. (RBP), is developing RBP-6000, a long-acting formulation of buprenorphine for monthly SC administration, for the treatment of opioid use disorder.

### **2.1 Primary Objective**

To assess the long-term safety and tolerability of RBP-6000 subcutaneous (SC) injections in subjects with opioid use disorder.

### **2.2 Secondary Objectives**

To collect clinical outcome data with RBP-6000 SC injections in subjects with opioid use disorder.

### **2.3 Tertiary Objectives**

To evaluate the:

- PK of RBP-6000,
- Relationship between RBP-6000 PK and clinical outcome data, and
- Impact of RBP-6000 on health and economic outcomes.

### 3 INVESTIGATIONAL PLAN

#### 3.1 Overall Study Design and Plan

This is a multicenter, open-label, long-term safety study in which approximately 600 subjects diagnosed with opioid use disorder will be enrolled (approximately 300 subjects who did not participate in the RB-US-13-0001 study [hereafter referred to as “*de novo*” subjects] and approximately 300 subjects that completed the RB-US-13-0001 study [hereafter referred to as “roll-over” subjects]). Subject participation will be based on the Investigator’s determination that initiation or continuation of study treatment is appropriate; and, that among subjects who are continuing from the RB-US-13-0001 study, there have been no significant protocol deviations or clinically relevant AEs that would preclude inclusion of the subject in this study. All subjects will need to provide written informed consent before any protocol-related procedures commence. At the Screening Visit (which is up to 3 days after the End of Study [EOS] Visit (Day 169 + 3)), for roll-over subjects), potential subjects will be reviewed for eligibility against inclusion and exclusion criteria, and eligible subjects will be enrolled into the trial.

Before receiving the first injection of RBP-6000 in this safety study, all subjects will undergo a Run-In period with SUBOXONE® (buprenorphine/naloxone) sublingual film to avoid precipitating a withdrawal syndrome and to preserve the blind in subjects treated with placebo in the RB-US-13-0001 study. Subjects will be inducted onto SUBOXONE sublingual film consistent with the SUBOXONE sublingual film label; they will then complete a 1 to 11 day SUBOXONE sublingual film Dose Adjustment period ([Section 5.2.1](#)). SUBOXONE dose adjustments will be made based on COWS scores as well as physician judgment ([Section 5.2.2](#)).

Once subjects meet the criteria (on Day -11 to Day -1) of no significant opioid craving ( $\leq 20$  mm on the Opioid Craving Visual Analog Scale [VAS] and no significant withdrawal ( $\leq 12$  on the Clinical Opiate Withdrawal Scale [COWS]) they may receive the first SC injection of RBP-6000 (containing 300 mg buprenorphine). Subjects with significant withdrawal signs/symptoms (defined as  $>12$  on the COWS) or significant cravings for opioids (defined as  $>20$  mm on the Opioid Craving VAS) after the end of the 2-week SUBOXONE sublingual film Run-In period will not be eligible to continue in the study and will be referred for treatment.

On Day 1 of the study (initiation of study drug injections), all subjects will receive a SC injection of 300 mg of buprenorphine in RBP-6000. Subsequent doses of RBP-6000 may be adjusted down to 100 mg and back up to 300 mg based on the medical judgment of the Investigator. After injection of RBP-6000, subjects will not be permitted to receive supplemental SUBOXONE sublingual film during the RBP-6000 treatment period. Subjects who require supplemental SUBOXONE sublingual film or other sublingual buprenorphine pharmacotherapy during the RBP-6000 treatment period will be withdrawn from the study and referred for appropriate treatment.

Subjects will return to the clinic for monthly injection visits (every 28 - 2/+ 4 days) for a total of up to 12 injections for *de novo* subjects or for a total of 6 injections for roll-over subjects. ECG recordings and vital signs will be collected pre and post each SC injection. All ECGs will be interpreted by a central monitoring facility. Subject-reported injection site pain Visual Analog

Scale scores (VAS) will be collected at various times up to 1 hour after each injection. Local injection site grading will be collected at various time points starting immediately after injection and will be evaluated for pain, tenderness, warmth, itching, erythema, inflammation or swelling, and bruising using a 4-point severity scale. At each visit after injections begin, the injection site will be assessed by site staff and will also be evaluated for evidence of attempts to remove the depot.

Subjects will need to return to the clinic weekly for the first 5 weeks and biweekly (i.e., every 2 weeks) until injection 6, and monthly for the rest of the study period for urine drug screens (UDS), Timeline Followback (TLFB) interviews, opioid craving VAS evaluation, COWS and subject reported outcomes (Subjective Opiate Withdrawal Scale [SOWS]). Subjects will continue to receive counseling (manual-guided behavioral therapy) during the study.

Safety assessments will be collected at each visit and will include the following: vital signs, electronic Columbia Suicide Severity Rating Scale (eC-SSRS) responses, ECGs, laboratory tests (hematology, chemistry, urinalysis, and pregnancy test), concomitant medications, and AEs.

Sparse PK blood samples will be collected for population PK analysis for the roll-over subjects only. Once at least 75 roll-over subjects have completed Injection 6 (Week 25, Day 169) the sites will be notified that no more PK samples will be required to be collected from the roll-over subjects for the duration of the study. PK samples will not be collected for the *de novo* subjects. However, for all subjects (*de novo* and roll-over) throughout the study, a PK sample will be taken as soon as possible after any SAE is reported. If possible, an additional sample should be collected when the SAE has been resolved. ECGs will be performed before PK sample collection. The following depression, pain, and health economic outcome assessments will also be collected: Beck Depression Inventory (BDI-II), brief pain inventory (BPI), EuroQol EQ-5D-5L (EQ-5D-5L), 36-Item Short Form Health Survey, Version 2 (SF-36v2), Medication Satisfaction Questionnaire (MSQ), healthcare resource utilization (HCRU), Treatment Effectiveness Assessment (TEA) and Addiction Severity Index Lite (ASI-Lite).

Approximately 2 months prior to the scheduled EOS visit, the subject's ongoing treatment options will be reviewed with the investigator. At the EOS, 2 transition treatment options may be offered if the subject is eligible:

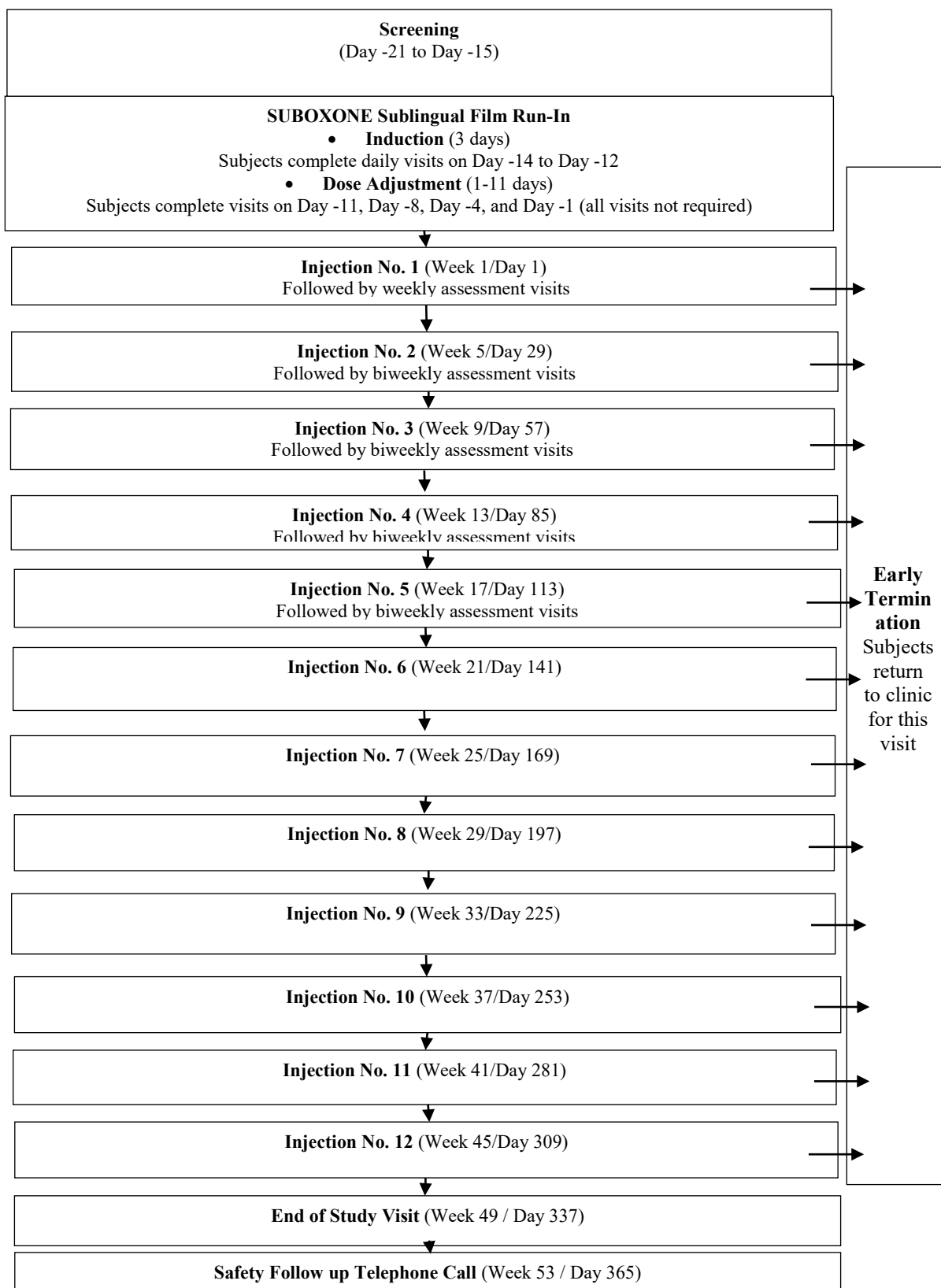
- Subjects who complete the RBP-6000 treatment period may be offered entry into an open label extension study of RBP-6000 (Study INDV-6000-301). Eligibility will be based on meeting the inclusion and exclusion criteria and the medical judgment of the Investigator.
- Subjects who do not meet the eligibility criteria of the extension study, or subjects who do not wish to enroll may alternatively enter a 4-week SUBOXONE transition period if deemed suitable by the investigator. Subjects should be dosed using the Investigators medical judgement. Any additional unscheduled visits required by the subject for the SUBOXONE transition will not be compensated by the Sponsor.

Subjects that have not enrolled onto the INDV-6000-301 should be contacted by telephone approximately 4 weeks after EOS for a safety follow-up assessment of AEs and use of concomitant medications.

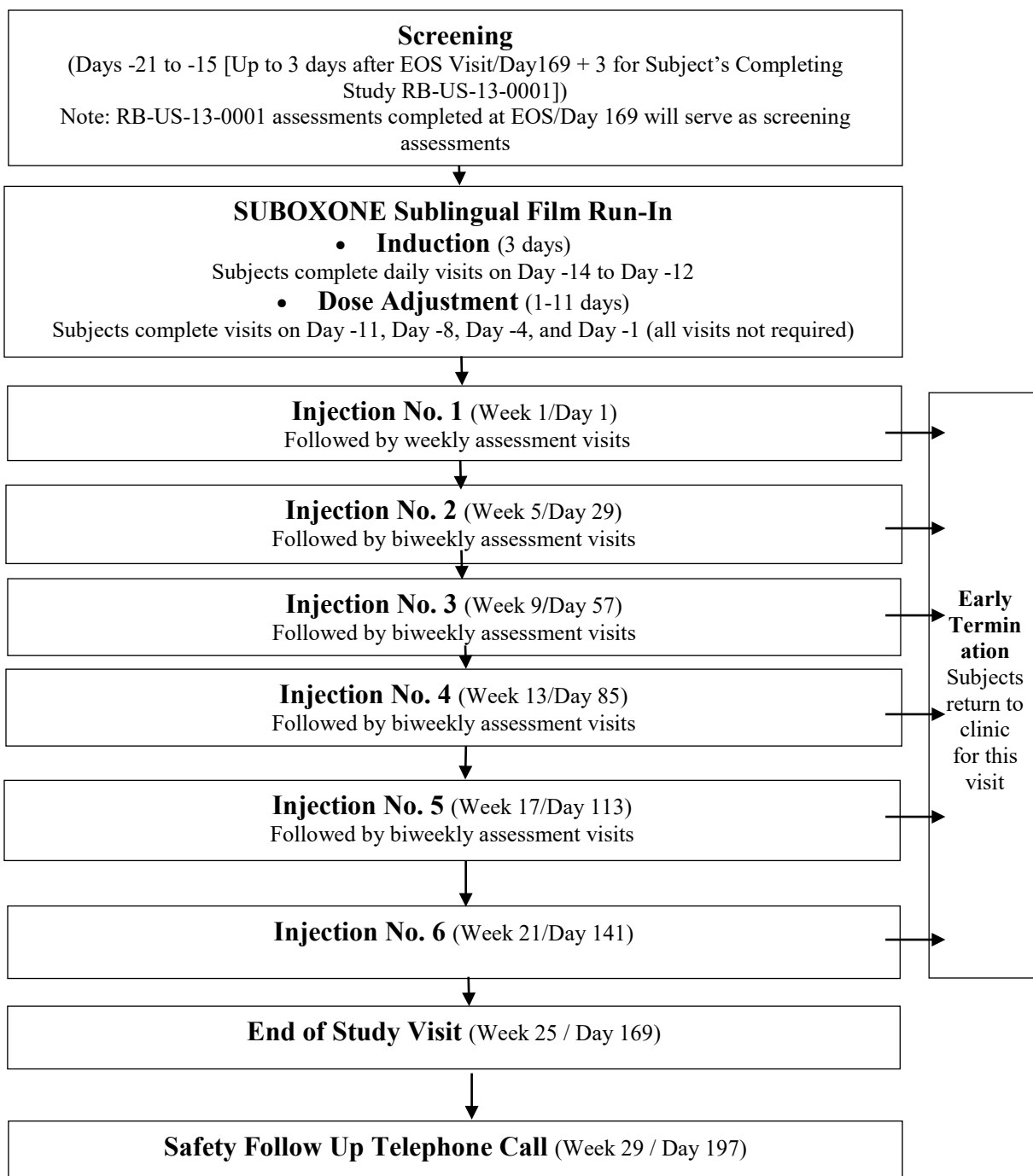
A schematic depicting the study design for *de novo* subjects is in [Figure 2](#) and a schematic for roll-over subjects is in [Figure 3](#). A complete list of procedures and assessments for subjects is in the Schedule of Events (SOE) in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#).



**Figure 2 Study Overview: *De novo* Subjects**



**Figure 3 Study Overview: Roll-over Subjects from RB-US-13-0001**



### 3.2 Rationale for Study Design

This study is designed to assess the long-term safety, tolerability, and clinical outcomes of RBP-6000 SC injections in subjects with opioid use disorder. The planned number of subjects was designed to ensure at least 100 subjects reach 1 year of treatment with RBP-6000 (as advised in the ICH-E1A Guideline - The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions). The safety assessments used include evaluations of AEs, serious AEs (SAEs), discontinuations from study due to AEs; local injection site tolerability (e.g., injection site grading); injection site pain using a subject-reported VAS; suicidality using the eC-SSRS, concomitant medications; changes in clinical laboratory results; vital sign measurements; 12-lead ECGs, and physical examination results. The instruments used to measure clinical outcomes (e.g., COWS, SOWS, Opioid Craving VAS, and eC-SSRS) were developed to measure the specific symptoms exhibited by and the challenges facing opioid-dependent individuals.

### 3.3 Study Duration and Dates

The expected maximum duration of participation for *de novo* subjects is up to approximately 55 weeks consisting of up to a 7-day screening period, up to a 14-day SUBOXONE sublingual film Run-In, up to a 48-week open-label treatment period, and a 4-week safety follow-up telephone call.

The expected maximum duration of participation for roll-over subjects is up to approximately 31 weeks, consisting of up to a 7-day screening period, up to a 14-day SUBOXONE sublingual film Run-In, a 24-week open-label treatment period, and a 4-week safety follow-up telephone call.

Subjects who enroll in the INDV-6000-301 study at the EOS visit are not required to be contacted with a safety follow-up telephone call.

Subjects who receive at least 1 dose of RBP-6000 and discontinue the trial for any reason will be required to complete the Early Termination (ET) visit.

If a sufficient number of subjects reach 1 year of exposure to RBP-6000, the study may be stopped early, and all remaining subjects will complete EOS procedures.

## 4 STUDY POPULATION SELECTION

### 4.1 Study Population

Approximately 300 *de novo* subjects will be enrolled into this study as well as approximately 300 roll-over subjects. The study population will consist of individuals diagnosed with opioid use disorder who are seeking treatment.

### 4.2 Inclusion Criteria

A. **De novo Subjects:** Subjects who have not participated in Study RB-US-13-0001 must meet the following criteria to be enrolled in this study:

1. Subjects seeking treatment for opioid use disorder who currently, and by medical history over the previous 3 months, meet the DSM-5 criteria for moderate or severe opioid use disorder.
2. Subjects who provide written informed consent to participate in this study.
3. Subjects who are an appropriate candidate for opioid partial-agonist treatment in the opinion of the Investigator or medically responsible physician.
4. Either male or female.
5. Age  $\geq 18$  to  $\leq 65$  years.
6. Have a body mass index (BMI) of  $\geq 18.0$  to  $\leq 35.0$  kg/m<sup>2</sup>.
7. **Females:** Women of childbearing potential (defined as all women who are not surgically sterile or postmenopausal for at least 1 year prior to informed consent), must have a negative pregnancy test prior to enrollment and must agree to use a medically acceptable means of contraception from screening through at least 6 months after the last dose of investigational medicinal product (IMP).

**Males:** Subjects with female partners of child-bearing potential must agree to use medically acceptable contraception after signing the informed consent form (ICF) through at least 6 months after the last dose of IMP. Male subjects must also agree not to donate sperm during the study and for 6 months after receiving the last dose of IMP.

The following methods of contraception are 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.

8. Subjects must agree not to take any buprenorphine products other than those administered during the current study throughout participation in the study.
9. Subjects must be willing to adhere to study procedures.

B. **Roll-Over Subjects:** Subjects who have successfully completed Study RB-US-13-0001 in its entirety must complete EOS/Day 169 assessments, which will serve as screening for this study. In addition, **only** the following criteria must be met to be enrolled in this study:

1. Provide written consent to participate in this study.
2. Be considered eligible in the medical judgment of the Investigator.

3. Females: Women of childbearing potential (defined as all women who are not surgically sterile or postmenopausal for at least 1 year prior to informed consent) must have a negative pregnancy test prior to enrollment and must agree to use a medically acceptable means of contraception from screening through at least 6 months after the last dose of IMP.

Males: Subjects with female partners of child-bearing potential must agree to use medically acceptable contraception after signing the ICF through at least 6 months after the last dose of IMP. Male subjects must also agree not to donate sperm during the study and for 6 months after receiving the last dose of IMP.

The following methods of contraception are 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.

4. Subjects must agree not to take any buprenorphine products other than those administered during the current study throughout participation in the study.

5. Subjects must be willing to adhere to study procedures.

### 4.3 Exclusion Criteria

A. ***De novo* Subjects** who meet any of the following criteria will be excluded from the study:

1. Current diagnosis, other than opioid use disorder, requiring chronic opioid treatment.
2. Current substance use disorder, as defined by DSM-5 criteria, with regard to any substances other than opioids, cocaine, cannabis, tobacco, or alcohol.
3. Positive UDS result at screening for cocaine or cannabis AND meets DSM-5 criteria for either moderate or severe cocaine or cannabis use disorder, respectively.
4. Meets DSM-5 criteria for moderate or severe alcohol use disorder.
5. Treatment for opioid use disorder required by court order.
6. Current incarceration or pending incarceration/legal action that could interfere with a subject's ability to participate in the study.
7. Pregnant or lactating females.
8. Current use of prescription or OTC medications that are 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 are provided in the excluded medications list ([Appendix 9](#)).
9. 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.
10. 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.
11. Clinically significant abnormal systolic blood pressure (BP) or diastolic BP, in the opinion of the Investigator.

12. Uncontrolled medical or psychiatric illness that, in the opinion of the Investigator or Sponsor, may place the subject at risk or interfere with outcome measures or a subject's ability to participate in the study.
13. 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 place the subject at risk or interfere with outcome variables.
14. History or presence of allergic or adverse response (including rash or anaphylaxis) to buprenorphine, naloxone, or the ATRIGEL Delivery System.
15. Total bilirubin  $\geq 1.5$ x the upper limit of normal (ULN), alanine aminotransferase (ALT)  $\geq 3$ xULN, aspartate aminotransferase (AST)  $\geq 3$ xULN, serum creatinine  $> 2$ xULN, international normalized ratio (INR)  $> 1.5$ xULN, lipase  $> 3$ xULN, amylase  $> 3$ xULN, or any abnormal pancreatic enzyme value above ULN that is associated with clinically significant, active pancreatic disorder.
16. Congenital long QT syndrome, history of prolonged QT in the 3 months prior to screening, or a corrected QT interval (Fridericia's – QTcF)  $> 450$  msec (male) or  $> 470$  msec (female) or history of risk factors for Torsades de Pointes.
17. Diagnosis of acquired immunodeficiency syndrome (AIDS).
18. Affiliated with, or a family member of, site staff directly involved in the study.
19. Unable, in the opinion of the Investigator or the medically responsible physician, to comply fully with the study requirements.
20. Clinically significant anemia or low hemoglobin (levels  $< 9$  g/dL) at Screening.
21. Donation of  $> 250$  mL of blood or plasma within the 30 days prior to providing written informed consent
22. Participation in any other clinical trial within 30 days prior to informed consent
23. Received medication-assisted treatment for opioid use disorder (e.g., methadone, buprenorphine) in the 90 days prior to providing written informed consent
24. Previously received RBP-6000.
25. Use of (within the past 30 days prior to providing written informed consent) or positive UDS result at screening for barbiturates, benzodiazepines, or methadone.

**B. Roll-Over Subjects** who meet any of the following criteria will be excluded from the study:

1. Discontinued early from Study RB-US-13-0001
2. Experienced any major protocol deviations or adverse events during the RB-US-13-0001 study which, in the opinion of the Investigator, could potentially compromise subject safety.
3. Women of childbearing potential who have a positive pregnancy test at EOS/Day 169, who are pregnant or breastfeeding, seeking pregnancy, or failing to use adequate contraceptive methods during the study.

#### **4.4 Day -1/Enrollment Criteria**

Beginning on the 4th day of SUBOXONE sublingual film dosing (Study Day -11) through the 14th day of dosing, subjects will be evaluated for Day -1 criteria. Subjects must meet the following criteria in order to be enrolled:

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  $\leq 12$ .
4. Opioid Craving VAS score of  $\leq 20$  mm.

## 5 STUDY TREATMENTS

### 5.1 Description of Treatments

#### 5.1.1 SUBOXONE Sublingual Film

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo. Each SUBOXONE sublingual film contains buprenorphine HCl and naloxone HCl dihydrate at a 4:1 ratio expressed as the free bases. Films are intended for SL administration and are available in 4 dosage strengths (2 mg/0.5 mg; 4 mg/1 mg; 8 mg/2 mg; and 12 mg/3 mg).

#### 5.1.2 Investigational Medicinal Products

RBP-6000 uses buprenorphine base in the ATRIGEL Delivery System, which is currently used in a number of approved commercial products. RBP-6000 will be supplied as a single-syringe system, which is prefilled with RBP-6000. The entire contents of the prefilled syringe will be administered. (See [Appendix 8: Study Drug Preparation and Dispensing Procedures](#) for detailed dosage instructions).

RBP-6000 is manufactured by Indivior Inc. according to Good Manufacturing Practice standards.

All used syringes components will be disposed of in accordance with the site's standard operating procedures (SOP) or pharmacy destruction policy. The site's clinical research associate (CRA) will review the site's SOP and/or pharmacy destruction policy. All IMP packaging will be retained for CRA verification.

### 5.2 Treatments Administered

#### 5.2.1 Run-In Treatment Period

##### 5.2.1.1 SUBOXONE Sublingual Film Induction (*De novo* Subjects)

*De novo* subjects will receive their first dose of SUBOXONE sublingual film on Induction Day 1. Subjects will be started with an initial dose of 2 mg/0.5 mg or 4 mg/1 mg and may titrate upwards in 2 or 4 mg increments of buprenorphine, at approximately 2-hour intervals, under clinical supervision, to 8 mg/2 mg based on therapeutic response.

On Induction Day 2, subjects with a COWS score > 12, or subjects reporting withdrawal signs/symptoms overnight, will receive a dose of SUBOXONE sublingual film equal to the total dose given on Induction Day 1 plus 4 mg. (For example, if a subject received a total dose of 8 mg on Induction Day 1, the starting dose of buprenorphine for Induction Day 2 would be 12 mg). If the COWS score is still > 12 one hour later, another 4 mg dose can be given. The subject should not exceed a maximum dose of 16 mg/4 mg for Induction Day 2. Subsequent SUBOXONE sublingual film doses must be separated by at least 1 hour from the preceding dose. SUBOXONE sublingual film doses may also be adjusted downward if necessary.



On Induction Day 3, subjects will be titrated to therapeutic response based on COWS scores as well as physician judgment. Most subjects will only require a single dose on Induction Day 3 which will equal the Induction Day 2 dose or the Induction Day 2 dose plus 4 mg buprenorphine. Additional doses may also be administered on Induction Day 3 (up to 24 mg). Subsequent SUBOXONE sublingual film doses must be separated by at least 1 hour from the preceding dose. Subjects should reach a daily dose of between 8 mg/2 mg and 24 mg/6 mg by Induction Day 3 and continue on that dose through the remainder of the SUBOXONE sublingual film Run-In period, with additional dose adjustments if necessary.

The SUBOXONE sublingual film(s) will be administered under the tongue, close to the base on the left or right side, until they are dissolved. If an additional sublingual film is required, it should be placed on the opposite side from the first film. Subjects should be instructed to hold the films under the tongue until they dissolve. If a third film is required, it should be placed under the tongue after the first 2 films have dissolved.

For more information about SUBOXONE sublingual film administration, please refer to the SUBOXONE Full Prescribing Information (See [Appendix 7](#)).

#### 5.2.1.2 SUBOXONE Sublingual Film Induction (Roll-over Subjects)

Following screening, roll-over subjects will be inducted on SUBOXONE sublingual film to achieve daily doses between 8 mg to 24 mg buprenorphine according to the SUBOXONE sublingual film prescribing instructions. Roll-over subjects may start their SUBOXONE run in on the same day that they complete the RB-US-13-0001 EOS visit (and up to 7 days after this date) provided they meet the appropriate inclusion criteria and do not meet any exclusion criteria. Subjects must be titrated to a **minimum dose of 8 mg** SUBOXONE by the end of the 3-day Induction period regardless of their COWS scores and/or the presence or absence of withdrawal symptoms.

Subjects will receive their first induction dose on Induction Day 1. Subjects should be started with an initial dose of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone and may titrate upwards in 2 or 4 mg increments of buprenorphine, at approximately 2-hour intervals, under supervision, to a total dose of up to 8 mg/2 mg buprenorphine/naloxone based on the control of acute withdrawal symptoms.

On Induction Day 2, subjects with a score for COWS of > 12, or subjects reporting opioid withdrawal signs/symptoms overnight, should receive a dose of study drug equal to the total dose given on Induction Day 1 plus 4 mg. If the COWS score is still > 12 one hour later, another 4 mg dose can be given. The subject should not exceed a maximum dose of 16 mg/4 mg buprenorphine/naloxone for Induction Day 2. Subsequent SUBOXONE sublingual film doses must be separated by at least 1 hour from the preceding dose. SUBOXONE sublingual film doses may also be adjusted downward if necessary.

On Induction Day 3, subjects will be titrated to therapeutic response until a therapeutic dosage is reached, based on COWS scores as well as physician judgment. Most subjects will only require a single dose on Induction Day 3 which will equal the Induction Day 2 dose or the Induction Day 2 dose plus 4 mg. Additional doses may also be administered on Induction Day 3 (up to 24 mg).

Subsequent SUBOXONE sublingual film doses must be separated by at least 1 hour from the preceding dose. Although subjects should reach a daily dose of between 8 mg and 24 mg by Induction Day 3 and continue on that dose through the remainder of the SUBOXONE sublingual film Run-In period, dose adjustments may be necessary during the Run-In period.

The SUBOXONE sublingual film(s) will be administered under the tongue, close to the base on the left or right side, until they are dissolved. If an additional sublingual film is required, it should be placed on the opposite side from the first film. Subjects should be instructed to hold the films under the tongue until they dissolve. If a third film is required, it should be placed under the tongue after the first 2 films have dissolved.

For more information about SUBOXONE sublingual film administration, please refer to the SUBOXONE Full Prescribing Information (See [Appendix 7](#)).

### 5.2.2 Dose Adjustment Period (All Subjects)

Beginning at Day -11, subjects will be assessed to determine whether they meet Day -1 /enrollment criteria as defined in Section 4.4. Once subjects meet the enrollment criteria (no significant opioid craving ( $\leq 20$  mm on the Opioid Craving Visual Analog Scale [VAS] and no significant withdrawal ( $\leq 12$  on the Clinical Opiate Withdrawal Scale [COWS]), they are eligible to receive the first SC injection of RBP-6000 (containing 300 mg buprenorphine). Subjects with significant withdrawal signs/symptoms (defined as  $>12$  on the COWS) or significant cravings for opioids (defined as  $>20$  mm on the Opioid Craving VAS) after the end of the 2-week SUBOXONE sublingual film Run-In period will not be eligible to continue in the study and will be referred for treatment.

### 5.2.3 Active Study Treatment

On Day 1 of the study (initiation of study drug injections), all subjects will receive a SC injection of 300 mg of buprenorphine in RBP-6000. Subsequent doses of RBP-6000 may be adjusted down to 100 mg and back up to 300 mg based on the medical judgment of the Investigator. All subjects will receive injections of RBP-6000 separated by 28 (- 2/+ 4) days.

After injection of RBP-6000, subjects will not be permitted to receive supplemental SUBOXONE sublingual film during the RBP-6000 treatment period. Subjects who require supplemental SUBOXONE sublingual film or other sublingual buprenorphine pharmacotherapy during the RBP-6000 treatment period will be withdrawn from the study and referred for appropriate treatment.

A single SC dose will be injected by an individual who is medically qualified to perform the procedure and delegated by the Principal Investigator to perform the task. Injections of RBP-6000 will be administered in the abdominal area below the waist but above the hip bone; more specifically, injection should occur in the region where the body curves at the side to about 2 inches from the middle of the abdomen with adequate amounts of subcutaneous tissue that does not have excessive pigment, nodules, lesions, or hair. RBP-6000 will form a solid polymer depot that contains the buprenorphine. As the depot degrades, buprenorphine will be released

into the systemic circulation at a consistent rate over an approximately 28-day period. For detailed instructions on use, see [Appendix 8](#).

Approximately 2 months prior to the scheduled EOS visit, the subject's ongoing treatment options will be reviewed with the investigator. At the EOS, 2 transition treatment options may be offered if the subject is eligible:

- Subjects who complete the RBP-6000 treatment period may be offered entry into an open label extension study of RBP-6000 (Study INDV-6000-301). Eligibility will be based on meeting the inclusion and exclusion criteria and the medical judgment of the Investigator.
- Subjects who do not meet the eligibility criteria of the extension study, or subjects who do not wish to enroll may alternatively enter a 4-week SUBOXONE transition period if deemed suitable by the investigator. Subjects should be dosed using the Investigators medical judgement. Any additional unscheduled visits required by the subject for the SUBOXONE transition will not be compensated by the Sponsor.

### 5.3 Selection and Timing of Dose for Each Subject

The study schedule is designed so that each of the injections will be separated by a minimum of 26 days and a maximum of 32 days (28 days - 2/+ 4 days) and will be given on alternate sides of the subject's abdomen (see [Appendix 8](#) and the Pharmacy Manual for detailed information on administration).

### 5.4 Method of Assigning Subjects to Treatment Groups

When a *de novo* or roll-over subject signs the ICF, she/he will be assigned a unique subject number in numerical sequence, which will be used for the duration of the study. Roll-over subjects will retain the subject number assigned to them in the RB-US-13-0001 study. *De novo* subjects will be assigned a unique subject number, consisting of the site number followed by 9 and a 3 digit number in numerical sequence (e.g., the first *de novo* subject screened at site # 001 will be assigned the number 0019001). The subject number will be recorded in the source document and electronic case report form (eCRF).

All subjects will be assigned to receive the 300 mg RBP-6000 dose. Subsequent doses of RBP-6000 may be adjusted down to 100 mg and back up to 300 mg based on the medical judgment of the Investigator

### 5.5 Blinding

Not applicable; this is an open-label study

### 5.6 Concomitant Therapy

Concomitant therapies are defined as prescribed medications and OTC preparations, including herbal preparations and vitamins, other than study medication and supplementary medication that the subject receives within 30 days of screening and for the during the course of the study.

Concomitant medications that are ongoing at the time a subject rolls-over from the RB-US-13-0001 study will be recorded in the eCRF. Any medication taken by the subject is to be reported by the subject and noted on the subject's source document and concomitant medication page. Any changes in concomitant therapy during the study will be documented, including cessation of therapy, initiation of therapy, and dose changes.

Roll-over subjects who started on a benzodiazepine during the RB-US-13-0001 study will be evaluated on a case-by-case basis for inclusion in the RB-US-13-0003 study. The investigator will discuss these subjects with the medical monitor before enrolling into the RB-US-13-0003 study.

The Investigator or designee will also record any medications given for the treatment of AEs on the concomitant medication page.

#### 5.6.1 Permitted Concomitant Medications

Following screening and enrollment, ancillary medications (ibuprofen, acetaminophen, methocarbamol, hydroxyzine, and loperamide) may be administered to subjects to help alleviate signs and symptoms of opioid withdrawal as deemed necessary by the Investigator or medically qualified sub-investigator. Details on acceptable administration of these medications and preparations are provided below:

- Ibuprofen (400 mg orally) may be given every 4 to 6 hours as needed for pain up to a maximum of 2400 mg per day. Subjects for whom ibuprofen is contraindicated or not tolerated may be given acetaminophen (325 to 1000 mg every 4 to 6 hours) as needed up to a maximum of 3000 mg per day. Caution should be exercised when using acetaminophen concomitantly with other medications that have potential hepatotoxic effects. Methocarbamol may also be given as needed for relief of muscle pain in clinically appropriate doses based on physician assessment.
- Hydroxyzine (50 to 100 mg orally) may be given every 6 hours as needed for anxiety, nausea, or vomiting. Additionally, hydroxyzine (50 to 100 mg orally) may be given at bedtime as needed for sleep. The hydroxyzine daily dose should not exceed a maximum of 600 mg per day.
- Loperamide (2 to 4 mg orally) may be given as needed for diarrhea up to a maximum of 16 mg per day.

#### 5.6.2 Prohibited Concomitant Medications

Concomitant therapies subject to the restrictions indicated under Prohibited Concomitant Medications may be used only following approval by the Sponsor unless an immediate medical need necessitates their use. These are listed below:

- Use of buprenorphine.
- Ongoing prescription that are clinically relevant P450 3A4 inducers or inhibitors, such as azole antifungals (e.g., ketoconazole) and macrolide antibiotics (e.g., erythromycin).

- Herbal supplements that have the potential to cause prolongation of the QTc interval.
- Over-the-counter medications that have the potential to cause prolongation of the QTc interval. This does not apply to over-the-counter medications listed under Concomitant Therapies above that are prescribed by the Investigator, or over-the counter medications that may be used by the Investigator for an immediate medical need that necessitates their use. The medical monitor should be consulted for any questions.
- Medications, in the addition to those listed above, which may be expected to significantly interfere with the metabolism or excretion of buprenorphine that may be associated with a significant drug interaction with buprenorphine, or may pose a significant risk to subjects' participation in the study.

Other concomitant medications, OTC preparations, or therapies that are not allowed during study participation are listed in [Appendix 9](#).

## 5.7 Restrictions

### 5.7.1 Prior Therapy

All prior medications including OTC, dietary supplements, and herbal preparations taken by the subject within the 30 days prior to screening will be recorded.

### 5.7.2 Subject Activity Restrictions

Subjects should be advised to avoid strenuous exercise.

## 5.8 Protocol Compliance

This study involves the SC injection of multiple doses of RBP-6000 containing 100 or 300 mg of buprenorphine (see the Schedule of Events [SOE], [Appendix 2](#)). The Investigator may terminate a subject based on the subject's inability or willingness to comply with the protocol requirements.

IMP will be administered by designated and qualified study personnel at the site. The time and duration, the dose delivered, and any dosing observations will be recorded in source documentation. The Investigator or designated individual will maintain a log of all study drugs dispensed and returned (if applicable). Drug supplies will be inventoried and accounted throughout the study.

## 5.9 Packaging and Labeling

RBP-6000 will be packaged and labeled in a manner consistent with the study design and applicable regulations. The study medication will be provided to the investigator(s) by the Sponsor or contractor.

The SUBOXONE sublingual film will be supplied as bulk films in the following buprenorphine dosage strengths: 2mg /0.5 mg; 4 mg/1 mg; 8 mg/2 mg; and 12 mg/3 mg. Containers will be

labeled with a single panel disclosing the product name, lot number, contents, Sponsor name and address, route of administration, and appropriate precautionary statements.

The study drug, RBP-6000, will be identified as an investigational compound.

The following components will be used in the preparation of RBP-6000:

- One sealed foil pouch containing a syringe prefilled with RBP-6000 and an oxygen absorber pack.
- One sterile 19-gauge, 1 inch hypodermic safety needle.

## **5.10 Storage and Accountability**

RBP-6000 should be stored under refrigerated conditions between 2-8°C (36-46°F). Temperature excursions between 8 and 25°C (46 and 77°F) are permitted for a maximum duration of 48 hours; Temperature excursions between 2 and -20°C (-4 and 36°F) are permitted for a maximum duration of 7 days. Temperature excursions outside of these ranges or timeframes should be reported to the Sponsor immediately and approval for use should be obtained.

SUBOXONE sublingual films should be stored at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F). Temperature excursions outside of these ranges should be reported to the Sponsor immediately and approval for use should be obtained.

The PI or designee is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. Drug accountability is the responsibility of the PI or designee, with verification by the CRA. Study drug must be handled strictly in accordance with the protocol, handling guidelines and the label, and must be stored in a locked, limited access area under appropriate environmental conditions. The PI must ensure that proper conditions exist for storage of study treatments. The dispensing of study drug to the subject must be documented on the drug dispensing form.

Unused study drug must be available for verification by the Sponsor's site monitor during on-site monitoring visits. The return to the Sponsor of unused study drug will be documented on the Study Drug Return Form.

The Investigator agrees not to supply RBP-6000 to any person except study personnel for SC injection of subjects in this study.

## **5.11 Investigational Product Retention at Study Site**

The PI or medically-qualified designee agrees to conduct a study drug supply inventory for RBP-6000, to record results of this inventory, and to return all unused study drug to the Sponsor at times specified by Indivior. Indivior will arrange for the appropriate and timely destruction of all returned, unused RBP-6000. All used needles and syringes from RBP-6000 will be disposed of into an appropriate secure biohazard container per the standard operating procedures (SOPs) at the study site.

All used IMP packaging (e.g. carton, foil pouch) will be retained at the study site until reconciliation is performed by the CRA. After reconciliation is completed, the used IMP packaging may be disposed of per the SOPs at the study site.

## 6 STUDY PROCEDURES

The SOE for this study is provided in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#).

For roll-over subjects, study procedures completed at EOS/Day 169 for study RB-US-13-0001 will serve as screening assessments for the open-label study.

### 6.1 Informed Consent

#### 6.1.1 General Information

Prior to entering the study, the Investigator or designated individual must explain to each subject the nature of the study, its purpose, procedures, expected duration, alternative therapies available, and the benefits and risks involved in study participation. Subjects must be given the Institutional Review Board (IRB)-approved ICF version to review and the opportunity to ask questions. Subjects must be informed of their right to withdraw from the study at any time without prejudice. The potential subjects should be able to answer simple questions about the study after the ICF has been reviewed and explained. After this explanation and before any study-specific procedures have been performed, the subject must voluntarily sign and date the ICF to indicate the desire to participate in the study. Prior to participation in the study, the subject must receive a copy of the signed and dated ICF.

Roll-over subjects will complete all Day 169/EOS procedures for study RB-US-13-0001 prior to signing the ICF for this study.

### 6.2 Medical History

For *de novo* subjects, a detailed medical history will be obtained by the PI or medically qualified designee during the screening visit (Visit 1). This will include information regarding the subject's full history of medical and psychiatric conditions, diagnoses, procedures, treatments, concomitant medications, demographic information, and use of tobacco, drugs of abuse, alcohol, and caffeine, and any other noteworthy medical information, including suicidality measured using the eC-SSRS. Any updates to medical history information that the PI or medically qualified designee becomes aware of will be captured throughout the study. All prior medications, OTC health, and dietary supplements taken by the subject within 30 days will be recorded. In addition, hospitalizations in the past 3 months and the reason for admission (medical/surgical/psychiatric/other) will be recorded.

For roll-over subjects, medical history will not be obtained again.

### 6.3 Physical Examination

A complete physical examination (PE) will be performed by the Investigator or medically qualified designee. The physical examination will consist of an examination of the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest and lungs, heart, abdomen, extremities, body weight, and a brief neurological assessment.



The examination will not include a pelvic, breast, or rectal examination. If any clinically significant abnormal findings started before the date that informed consent was given, these findings should be recorded on the Medical History case report form (eCRF).

If any clinically significant change from screening (Visit 1 for *de novo* subjects; Study RB-US-13-0001 EOS visit (Day 169) for roll-over subjects) is noted, it will be reported as an AE and followed up to resolution or until reaching a stable end point.

Weight (kg) will be assessed (in ordinary indoor clothing with shoes off) and will be recorded at screening as well as periodically throughout the study. Height (cm) will be recorded at screening only. BMI will be calculated at screening as well as periodically throughout the study. BMI is defined as the subject's weight in kg divided by the square of the subject's height in meters ( $\text{kg/m}^2$ ). The amount of abdominal fat will be measured using the waist-to-hip ratio and will be recorded at screening as well as periodically throughout the study.

Procedures performed at Day 169/EOS in the RB-US-13-0001 study will not be repeated at the screening visit for roll-over subjects.

Assessments are performed at the time points detailed in the SOEs ([Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#)).

## 6.4 Vital Signs

Evaluation of vital signs will be performed after the subject has been supine for  $\geq 3$  minutes and will include a measurement of systolic and diastolic BP, pulse rate, pulse oximetry, respiratory rate, and oral temperature.

If clinically significant findings, as determined by the Investigator or medically qualified sub-investigator, occur in any vital sign measurement, that measurement will be captured as an AE and repeated at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.

Assessments will be recorded in the source documents and eCRF and will be performed at the time points detailed in the SOE ([Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#)).

## 6.5 Electrocardiograms

### 6.5.1 12-Lead Electrocardiograms

Resting 12-lead ECGs will be recorded with the subject in supine position following a 10-minute rest period. For roll-over subjects, ECGs will be recorded prior to the PK blood sampling. ([Appendix 6](#)).

Resting 12-lead ECGs will be recorded as indicated in the SOEs ([Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#)). ECGs recorded at screening will be recorded in triplicate, at approximately 2 - 5 minute intervals.

ECG intervals including HR, QT, QTcF, QTcB, RR, PR, QRS and T wave changes will be recorded. ECGs will be reviewed by the Investigator during the visits for any immediate abnormalities. ECGs will also be reviewed by a central facility.

The findings of the ECGs as determined by the central facility will be assessed by the Investigator and marked as normal, abnormal-not clinically significant, or abnormal-clinically significant. All clinically significant abnormalities will be captured as AEs. In the event that a clinically significant AE related to an ECG assessment occurs during the study, the Investigator should contact the Indivior Medical Monitor.

## **6.6 Clinical Laboratory Tests**

### **6.6.1 Laboratory Parameters**

All clinical laboratory assessments will be performed by a clinical laboratory accredited by the College of American Pathologists or with a certificate of compliance (or certificate of waiver for CLIA-waived tests) issued by the Center for Medicare & Medicaid Services or Clinical Laboratory Improvement Amendments. The laboratory assessments will include routine and screening laboratory tests.

See the SOEs in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#) for the timing of the specific required laboratory tests which are listed in [Table 2](#).

Any abnormal hematology, chemistry, or urinalysis test result deemed clinically significant by the Investigator will be repeated, including test results obtained on the final study day. For any test abnormality deemed clinically significant, an AE will be recorded (unless the result was considered erroneous) and repeat analysis will be performed until resolution or until the Investigator determines that resolution of the laboratory abnormality is not expected.

Subjects will be in a seated or supine position during blood collection. Clinical laboratory panels are listed in [Table 2](#).

**Table 2 List of Laboratory Tests**

<u>Hematology:</u>	<u>Serum Chemistry:</u>
Hematocrit	Albumin
Hemoglobin	Alkaline phosphatase
Mean corpuscular hemoglobin	Alanine aminotransferase (ALT)
Mean corpuscular hemoglobin concentration	Amylase
Mean corpuscular volume	Aspartate aminotransferase (AST)
Platelet count	Blood urea nitrogen
Pancreatic enzymes	Calcium
Red blood cell count	Calculated creatinine clearance
White blood cell count with differential	Carbon dioxide
	Chloride
<u>Urinalysis:</u>	Creatinine
Appearance	Creatine kinase and subtypes
Bilirubin	Gamma-glutamyl transferase
Color	Globulin
Glucose	Glucose (non-fasting)
Ketones	High-density lipoprotein (HDL)
Leucocyte esterase	Immunoreactive trypsinogen
Microscopic examination of sediment <sup>a</sup>	Lactate dehydrogenase
Nitrite	Lipase
Occult blood	Low-density lipoprotein (LDL)
pH	Magnesium
Protein	Phosphorus
Specific gravity	Potassium
Urobilinogen	Sodium
	Total bilirubin
<u>Hormone Panel:</u>	Direct bilirubin
Adrenocorticotrophic hormone (ACTH) Follicle Stimulating Hormone	Total cholesterol
Testosterone (total and free)	Total protein
	Triglycerides
	Uric acid
<u>Pregnancy:</u>	<u>Urine Drug Screen (UDS):</u>
Urine Pregnancy (only for females not postmenopausal or surgically sterile for at least 1 year)	Opioids <sup>b</sup>
Serum Pregnancy	Cocaine
	Amphetamines
<u>Screening:</u>	Methadone
Hemoglobin A1c	Cannabinoids
HIV-1 and -2 antibodies	Barbiturates
PTT	Benzodiazepines
PT with INR	Methamphetamine
Serum pregnancy	Phencyclidine

Anti-HIV = human immunodeficiency virus antibodies; hCG = human chorionic gonadotropin; INR = international normalized ratio; IRT = immunoreactive trypsinogen; PT = prothrombin time; and PTT = partial thromboplastin time.

<sup>a</sup> Microscopic examination of sediment will be performed only if the results of the urinalysis evaluation are positive (microscopic examination may include but is not limited to WBC count, RBC count, casts, and crystals).

<sup>b</sup> Oxycodone may not show up in all opiate assays and should be assessed separately.

### 6.6.2 Sample Collection, Storage, and Shipping

All blood sampling will be by individual venipuncture or with the use of a saline lock. Blood and urine sample collection and processing procedures will be outlined in a separate reference manual to be provided to the site.

### 6.6.3 Reference Ranges

Up-to-date reference ranges for the above investigations must be obtained for the laboratory performing analyses prior to the start of the study and be updated as appropriate during the course of the study.

### 6.6.4 Laboratory Results Review

The Investigator will review the results and comment on the laboratory results sheet for all abnormal values, identifying those that are abnormal but not clinically significant as well as those that are significantly abnormal. The Investigator will sign and date the laboratory results sheet to indicate that the review has taken place.

**Clinical Laboratory Changes:** It is the Investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the Investigator on the laboratory report. For each abnormal laboratory test result, the Investigator needs to ascertain if this is a clinically significant abnormal change from baseline for that individual subject.

## 6.7 Pharmacokinetic Assessments

Blood samples for population PK analysis will be collected from roll-over subjects only at the time points indicated in the PK sampling schedule ([Appendix 6](#)). Once at least 75 roll-over subjects have completed Injection 6 (Week 25, Day 169) the sites will be notified that no more PK samples will be required to be collected from the roll-over subjects for the duration of the study. The plasma concentrations of buprenorphine and norbuprenorphine will be quantified using specific and validated liquid chromatography tandem mass spectrometry methods. A laboratory manual for PK sample collection, processing, storage, and shipping will be supplied.

However, for all subjects (*de novo* and roll-over) throughout the study, a PK sample will be taken as soon as possible after any SAE is reported. If possible, an additional sample should be collected when the SAE has been resolved.

The exact times (to the minute) of PK blood sampling as well as the exact times of drug administration will be recorded in the source and eCRF.

## 6.8 Administration of Study Drug

The study drug will be assigned by an IWRS system. Injections will be administered by a physician or suitably-qualified designee (e.g., physician, nurse, nurse practitioner, PA) who has been delegated to perform the task. Study drug will be supplied only to subjects participating in

the study. The Investigator agrees not to allow the study drug to be administered from, nor stored at, any site other than the study site agreed upon with the Sponsor.

See [Appendix 7](#) for detailed descriptions of dosing for the SUBOXONE sublingual film. Detailed instructions for the preparation and administration of RBP-6000 are in [Appendix 8](#).

If at an injection visit there is a safety concern with administration of RBP-6000, after discussion with the medical monitor or sponsor, dosing can be delayed up to one week. In the event this occurs, the subsequent doses will be delayed. There must be at least 26 days between injections of study medication.

All used syringe components will be disposed of into an appropriate secure biohazard container or per the SOPs at the study site.

All used IMP packaging (e.g., carton, foil pouch) will be retained at the study site until the CRA conducts a visit to perform reconciliation. After the reconciliation is completed, the used IMP packaging may then be disposed of per the SOPs at the study site.

Unused IMP and returned SUBOXONE sublingual film must be available for verification by the Sponsor's site monitor during on-site monitoring visits. The return of unused or used returned IMP for destruction will be documented on the drug return form.

## 6.9 Safety and Suicidality Assessments

Safety will be assessed by AEs, vital signs, ECGs, clinical laboratory assessments, local injection site grading scale, injection site pain VAS, and eC-SSRS responses. See the SOE for specific timing of assessments ([Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#)).

### 6.9.1 Local Injection Site Tolerability

#### 6.9.1.1 Injection Site Grading

Local injection site grading will be performed by the Investigator or a trained and qualified health care professional, according to the SOE in [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#). Injection sites will be assessed for pain, tenderness, erythema/redness, induration, or swelling. Local injection site tolerability will be assigned a severity grade, including none (grade 0), mild (grade 1), moderate (grade 2), severe (grade 3), or potentially life threatening (grade 4) utilizing the Injection Site Grading Scale in [Appendix 15](#). The local injection site grading assessment will be completed electronically on injection days immediately after each injection (within 10 minutes) and at 1 hour ( $\pm$  15 minutes). For Injection 1 only, local injection site grading will be completed 24 hours ( $\pm$  4 hours) after the injection.

#### 6.9.1.2 Injection Site Pain Visual Analogue Scale (VAS)

Injection site pain will be assessed by the subject at each injection visit electronically with a 100mm VAS scale, where 0 represents no pain and 10 represents maximum pain ([Appendix 16](#)). The injection site-pain VAS scores will be obtained (after the completion of the injection) within

1 minute and then at 5, 10, 15, 30, and 60 minutes ( $\pm 5$  minutes). The timing of the Injection Site Pain VAS should be measured from the end of the injection. In addition to rating pain levels by marking on the line the point they feel best represents their perception of their current state, the subject will also answer the following question with either a Yes or No: Are you currently experiencing any burning or stinging at the injection site?

## 6.9.2 Suicidality

### 6.9.2.1 Columbia Suicide Severity Rating Scale

The eC-SSRS will be administered according to the SOE in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#). The eC-SSRS is a questionnaire designed for assessment of suicidal ideation and behavior in adolescents and adults (Posner 2011). The questionnaire will be administered as an electronic, self-rated version (eC-SSRS). Clinical trial versions of the questionnaire are available for trial screening and follow-up visits. A sample section from the Baseline/Screening eC-SSRS and the follow-up eC-SSRS are presented in [Appendix 10](#) and [Appendix 11](#), respectively.

If a subject becomes suicidal during the study, the investigator should provide the appropriate treatment to the subject. If the suicidality is deemed to be related to IMP and it is within 14 days of an injection, the depot may be removed ([Section 6.14.1](#)).

The eC-SSRS should be completed prior to SUBOXONE and RBP-6000 injection and at approximately the same time each day  $\pm 2$  hours.

If, there is a positive on the eC-SSRS after screening the subject will be evaluated by the investigator for continuation in the study. If needed, the investigator can consult with the medical monitor on continuation in the study of subjects with a positive eC-SSRS.

## 6.10 Adverse Events Assessments

### 6.10.1 Definition

In accordance with ICH and US FDA guidance, any untoward medical occurrence incurred by a subject that occurs after the first study-related procedure to the completion of the last EOS/ET visit or start of treatment on the INDV-6000-301 study and is associated with the use of the drug, regardless of the presence of causal relationship, is a reportable AE. AEs that are ongoing at the time a subject rolls-over from the RB-US-13-0001 study will be recorded in the eCRF.

Abnormal results of diagnostic procedures, including laboratory test abnormalities, are considered AEs if they:

- Result in discontinuation from the study,
- Require treatment or any other therapeutic intervention,
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality), or

- Are associated with clinical signs or symptoms that would have a significant clinical impact, as determined by the Investigator.

### 6.10.2 Performing Adverse Events Assessments

The Investigator is ultimately responsible for assessing and reporting all AEs as outlined in the protocol. The assessment of AEs may be delegated to a medically qualified sub-investigator, trained on this study protocol, who is listed on the FDA Form 1572 or equivalent document, and on the delegation of authority form.

AEs should be volunteered by the subject or solicited from the subject using a standard statement, obtained from examination of the subject at a clinic visit, or from observations of clinically significant laboratory values or special examination abnormal values. If an event assessed by one of the study scales requires intervention, or if in the opinion of the Investigator, it is clinically significant, then it will be reported as an AE.

All AEs are to be assessed and recorded in a timely manner and followed to resolution or until the Investigator determines that there is not an anticipated resolution. Each AE is to be documented with reference to severity, date of occurrence, duration, treatment, and outcome. Furthermore, each AE is to be classified as being serious or non-serious. In addition, the Investigator must assess whether the AE is drug-related or not. Changes in severity of AEs should be documented as one event at the maximum severity that occurred during the study.

### 6.10.3 Timing

AEs will be captured from the time the subject gives informed consent until the subject completes the study.

Surgical procedures, planned before enrollment of the subject in the study, are not considered AEs if the condition was known before study inclusion. In this case the medical condition should be reported in the subject's medical history.

If a subject experiences the onset of an SAE within 30 days following study completion and in the opinion of the Investigator, that SAE is associated with the study, it will be followed and reported as described in Section [6.10.9.2](#).

If a SAE occurs a PK sample will be taken as soon as possible after the event is reported. If possible, an additional sample should be collected when the SAE has been resolved.

### 6.10.4 Severity

Adverse events with changes in severity should be documented as one event at the maximum severity.

Intensity	Definition
Mild	Causes transient or mild discomfort ; no limitation of usual activities; no medical intervention required
Moderate	Causes mild to moderate limitation in activity; some limitation of usual activities: no or minimal medical intervention or therapy is required.
Severe	Causes marked limitation in activity; some assistance is usually required; medical intervention or therapy is required; hospitalization is probable.

The term “severe” is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as “serious,” which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

#### 6.10.5 Relationship

The Investigator or a medically qualified sub-investigator, trained on this study protocol, listed on the 1572 form or equivalent document and on the delegation of authority form is responsible for determining the AE relationship to the investigational product.

The following categories will be used to define the relationship of an AE to the administration of the investigational product:

- Not Related: Data are available to identify a clear alternative cause for the AE other than the investigational product.
- Related: The cause of the AE is related to the investigational product and cannot be reasonably explained by other factors (e.g., the subject’s clinical state, concomitant therapy, and/or other interventions).

#### 6.10.6 Expectedness

An unexpected AE is any AE, the nature and severity of which is not consistent with the applicable product information (e.g., Investigator’s Brochure for an investigational product or product label/summary of product characteristics for an approved product).

#### 6.10.7 Clinical Significance

The Investigator or medically qualified sub-investigator, trained on this study protocol, listed on the 1572 form or equivalent document and on the delegation of authority form is responsible for determining clinical significance of abnormal assessment results (e.g., laboratory or ECG results) for the subject.



### 6.10.8 Clinical Laboratory Adverse Events

Changes in laboratory values or vital signs, or other safety parameters (e.g., ECG, neurological and clinical symptom assessments) as noted in the protocol are a subset of AEs and are reportable only if considered to be clinically significant by the investigator or medically qualified sub-investigator except that:

- Baseline assessments are differentiated from AE/symptoms that are incurred post informed consent. These baseline lab assessments, if determined to be clinically significant abnormal values, reflect the status of the subject prior to study participation. These clinically significant pre-dose abnormal assessments without clinical symptoms will not be reported as AEs.

### 6.10.9 Serious Adverse Events

#### 6.10.9.1 Definition

A SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death,
- life-threatening AE,
- hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly or birth defect.

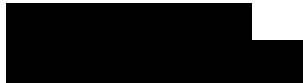
“Important medical events may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.”

#### 6.10.9.2 Reporting Serious Adverse Events

All SAEs must be reported to the Sponsor by the Investigator or designee by email or fax within 24 hours of discovery, using the form provided by the Sponsor. The SAE report should also be emailed to the Sponsor Medical Monitor.

In the event of an SAE, the Investigator or designee will notify Medical Monitor and the Indivior Pharmacovigilance:

Medical Monitor:



24-hour emergency number: (866) 326-5053

Email: [VAIL@prahs.com](mailto:VAIL@prahs.com)

Indivior Pharmacovigilance:

Email: [PatientSafetyNA@indivior.com](mailto:PatientSafetyNA@indivior.com)

Fax: (804) 423-8951  
Indivior Inc.  
10710 Midlothian Turnpike, Suite 430  
Richmond, VA 23235

The Investigator or designee must inform the IRB immediately regarding any AE (does not have to be causally related) that is both serious and unexpected; or that represents a series of AEs that on analysis is unanticipated, or occurs at an unanticipated frequency, or otherwise represents an unanticipated safety risk to the study subject. The IRB may subsequently choose to modify the informed consent or request changes to the protocol or Investigator's Brochure. A PK sample will be taken as soon as possible after any SAE is reported. If possible, an additional sample should be collected when the SAE has been resolved.

#### 6.10.10 Treatment-Emergent Adverse Events

A TEAE is an AE that either commenced following initiation of study drug or was present prior to the initiation of study drug, but increased in frequency or severity following initiation of treatment, regardless of causality.

#### 6.10.11 Procedures and Follow-Up of Subjects with Ongoing SAEs or Experiencing SAEs after Completion of or Withdrawal from the Study

Subjects with SAEs ongoing at the end of the study or after ET will be followed by the Investigator until stabilization or resolution. If a subject experiences the onset of an SAE within a period of 30 days following study completion or withdrawal and, in the opinion of the Investigator or medically qualified sub-investigator, it is associated with the study, it will be followed up and reported as described for other SAEs.

#### 6.10.12 Pregnancy

If a female subject believes she is pregnant (e.g., missed period, self-administered pregnancy test) the subject will be instructed to return to the clinical unit within 48 hours to undergo a serum pregnancy test. If a pregnancy in a subject is confirmed at any time during the study through a serum pregnancy performed by the study laboratory, the subject will be discontinued from the study and will undergo all final study visit procedures (with the exception of a urine pregnancy test). If the partner of a study subject becomes pregnant, the pregnancy will be reported to the clinical unit within 48 hours of the subject's knowledge of the pregnancy. The Investigator will attempt to collect pregnancy information on any female partner of a randomized male study subject who becomes pregnant while participating in this study. After obtaining the necessary signed informed consent from the female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to Indivior or designated representative within 24 hours of learning of the partner's pregnancy.

All confirmed pregnancies that occur within this study will be followed until resolution (i.e., termination [voluntary or spontaneous] or birth).

Pregnancy ([study subject or the partner of a study subject] [without associated unexpected or adverse sequelae]) is not a reportable AE but must be reported to the Sponsor within 24 hours of the Investigator or study staff first being aware of the subject's condition.

## 6.11 Clinical Outcome Assessments

Clinical outcome assessments will include the UDS for opioids and other drugs; self-reported use of illicit opioids, other drugs, and alcohol on the TLFB; COWS, SOWS, and Opioid Craving VAS.

### 6.11.1 Timeline Followback Interview

The TLFB Interview will be administered according to the SOE in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#). The TLFB Interview is a method to assess recent drug use and will be administered electronically. The questionnaire should be administered by an interviewer. The interview instrument asks subjects to retrospectively estimate their drug use in the 30 days prior to screen at the screening visit and since the last visit at all subsequent visits. Only occurrence of use is captured (i.e., used or did not use) (Fals-Stewart 2000). The interview takes approximately 10-30 minutes to complete and is appropriate for males and females 14 years of age and older. Drugs to be assessed in this study include opioids, methadone, buprenorphine, cocaine, barbiturates, benzodiazepines, amphetamines/methamphetamine, phencyclidine, and ethanol ([Appendix 17](#)).

The timeline followback interview should be completed prior to SUBOXONE and RBP-6000 injection and at approximately the same time each day  $\pm$  2 hours.

### 6.11.2 Opioid Craving Visual Analog Scale

The Opioid Craving VAS will be administered electronically according to the SOE in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#). A VAS is an instrument that measures a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. The amount of opioid craving that a subject feels for illicit opioids (not the buprenorphine used for treatment of opioid use disorder) can be recorded along a continuum from "no craving at all" to "strongest craving ever" (McMillan and Gilmore-Thomas 1996). Operationally, the VAS is a horizontal line, 100 millimeters (mm) in length, anchored by word descriptors at each end, as illustrated in [Appendix 14](#). The subject indicates the point on the line that he/she feels represents his/her perception of their current state. The VAS score is the difference from the left hand end of the line to the point that the subject marks and will be electronically calculated.

### 6.11.3 Clinical Opiate Withdrawal Scale

The COWS assessment will be administered electronically according to the SOE in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#). The COWS is an 11-item, validated instrument used to assess symptoms of opiate withdrawal (Wesson 2003, Tompkins 2009). The score is the sum of the response to each of the 11 items. The COWS is sometimes used by clinicians treating subjects with buprenorphine. A score of 5 to 12 is considered mild, 13 to 24 is

moderate, 25 to 36 is moderately severe, and a score of exceeding 36 is considered severe withdrawal. COWS scores will be electronically calculated. Each subject should be assessed by the same qualified and trained individuals throughout the course of the study as much as possible. This scale is presented in [Appendix 12](#).

#### 6.11.4 Subjective Opiate Withdrawal Scale

The SOWS (Handlesman 1987) will be administered electronically according to the SOE in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#). The SOWS is a 16-item scale completed by the subject and used to assess the subject's perception of opiate withdrawal symptoms. SOWS scores will be electronically calculated. This scale is presented in [Appendix 13](#).

### 6.12 Health Economics and Outcomes Assessments

Health economics and outcomes assessments will include: EQ 5D-5L, SF-36v2, MSQ, HCRU, TEA, ASI-Lite, BDI-II, and BPI.

All questionnaires will be completed at the appropriate study visits as indicated in the following sections.

#### 6.12.1 EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) and EQ-VAS

The EQ-5D-5L will be used to record subjects' health-related quality of life throughout the study at the time points indicated in the SOEs ([Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#)). It will be administered electronically.

The EQ-5D-5L is a widely-used, generic health-related quality of life instrument, which consists of 2 sections: the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS) ([Appendix 18](#)). The EQ-5D-5L is comprised of 5 questions/dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which can take 1 of 5 responses. The responses record 5 levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. EQ-5D-5L health states can be converted to a single summary index (range: 0-1) by using value sets that attaches values to each of the levels in each dimension. The EQ-VAS is a standard, vertical, 20 - cm visual analogue scale and will be used for recording a subject's rating for their current health-related quality of life state (Herdman 2007).

#### 6.12.2 Medical Outcomes Study Short Form-36 (SF-36v2)

The SF-36v2 is a generic, subject-reported outcome instrument used to assess quality of life, which will be administered electronically at the time points indicated in the SOEs ([Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#)).

The SF-36v2 is a 36-question instrument, which assesses 8 health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health

problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions ([Appendix 19](#)). The scale score of each domain is calculated based on the summed score across items included in the domain and is rescaled to 0 to 100 with higher scores indicating better health states.

The SF-36v2 provides scores for each of the eight health domains and psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores. The physical functioning, role physical, bodily pain, and general health can be used to construct a PCS score, while the vitality, social functioning, role emotional, and mental health scales are used to construct the MCS Scores (Ware 2007).

### 6.12.3 Medication Satisfaction Questionnaire (MSQ)

The MSQ is a single-item, patient-rated questionnaire ([Appendix 20](#)) that evaluates patient satisfaction with opioid medication. (Vernon 2010). Medication satisfaction will be measured with the MSQ at the time points indicated in the SOEs ([Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#)) electronically.

### 6.12.4 Healthcare Resource Utilization (HCRU) Questionnaire

The Healthcare Resource Utilization questionnaire will be completed by the Investigator or designee at the time points indicated in the SOEs ([Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#)). The HCRU will be used to collect current health insurance status, hospitalizations; residential substance abuse treatment; general practitioner, specialist, and counseling visits; and ED visits ([Appendix 21](#)). It will be administered electronically. The outpatient services captured on this questionnaire are ones conducted outside the study. Visits to the study site for scheduled study visits should not be reported here.

### 6.12.5 Treatment Effectiveness Assessment (TEA)

The TEA is a patient-reported instrument which will be measured at the time points indicated in the SOEs ([Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#)).

The TEA is a 4-item scale completed by the subject and used to assess the subject's perception of treatment effectiveness (Ling 2012). Patients respond to the TEA questions providing both numerical responses and brief feedback about their situation on four domains: substance use (drugs, alcohol, tobacco), health (e.g., physical, emotional health), lifestyle (e.g., housing or living situation, family, employment, relationships), and community (e.g., obeying laws and becoming a responsible member of society). The TEA scale is presented in [Appendix 22](#).

### 6.12.6 Addiction Severity Index (ASI) Lite

The ASI Lite is a patient-reported instrument that is conducted via interview by a team member trained in the administration of the ASI Lite. ASI Lite will be administered at the time points indicated in the SOEs ([Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#)). Given the nature of the ASI Lite, this instrument can be administered before or after injection of RBP-6000.

The ASI Lite, in an interview used to assess the subject's addiction severity, covers 7 potential problem areas: medical, employment/support status, alcohol, drug, legal, family/social, and psychiatric problems (Strain 1996). The ASI Lite interview text is presented in [Appendix 23](#). The ASI obtains lifetime information about problem behaviors, as well as problems within the previous 30 days. Of note, some items of the ASI Lite are only asked once at the initial visit; at subsequent time points only items indicated in the questionnaire should be administered.

Below is a brief description of each of the scales that will be included within the trial:

The medical status section of the ASI gathers basic information about the patient's medical history. It addresses information about lifetime hospitalizations, long-term medical problems and recent physical ailments. The employment/support status section of the ASI gathers information about the resources a patient can record on a job application, as well as his or her current sources of income. Many items will have a 30-day recall period regarding current employment. The drug/alcohol section of the ASI gathers information about the patient's substance abuse history. It addresses information about current and lifetime substance abuse, consequences of abuse, periods of abstinence, treatment episodes, and financial burden of substance abuse. While lifetime versions of these items are also available, this would only be assessed at first interview. The legal status section of the ASI gathers information about the patient's legal history. It addresses information about probation or parole, charges, convictions, incarcerations or detainments, and illegal activities. The family/social relationships section is designed to summarize the psychiatric, alcohol and drug abuse problems of the patient's relatives in each of the specified categories. The psychiatric problem section gathers information on psychiatric symptoms experienced by the patient.

#### 6.12.7 Beck Depression Inventory II (BDI-II)

Depression is highly prevalent in patients with opioid use disorders. Studies have been conducted using buprenorphine as a treatment for major depressive disorder.

The Beck Depression Inventory II (BDI-II) is used to measure the severity of depression in adults and adolescents. The BDI-II is scored on a 4 point Likert scale, each item ranging from 0-3; it has a 2 week recall period, can be self-administered or administered by interview and takes 5-10 minutes to complete.

The strengths of the BDI-II include its ease of use; also, it is widely known and the results are easy to score and interpret. The BDI-II has been successfully used to discriminate and measure depression in chronic pain patients on opioid therapy (Geisser 1997, Farren 2002, McCauley 2014).

The BDI-II assessment will be administered electronically according to the SOE in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#). This scale is presented in [Appendix 24](#). Roll-over subjects who did not complete the BDI-II at EOS/Day 169 will complete this assessment at the screening visit.

#### 6.12.8 Brief Pain Inventory (BPI) Short Form

A substantial number of patients in the US with opioid use disorder began by using prescription pain medications and subsequently developed dependence. Many of these patients are concerned

at the beginning of therapy that their pain may worsen when they are no longer taking their opioid medication.

The Brief Pain Inventory Short Form (BPI-SF) is used to measure the severity of pain and the impact of pain on daily functions in adults. The BPI-SF has a 24-hour recall period and can be self-administered or administered by an interviewer. It takes approximately 5 minutes to complete an instrument.

The BPI has been widely used to measure pain severity among opioid users (Rosenblum 2003). BPI-SF consists of a combination of yes/no questions, an item based on human figure drawing, open-ended questions, and items based on a numeric rating scale. Key strengths of the BPI-SF are that it is easy to administer and can provide rapid assessment of pain. BPI has been translated in many languages and is widely used. It captures all the components of pain: structural, intensity and its effect on patients.

The BPI assessment will be administered electronically according to the SOE in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#). This scale is presented in [Appendix 25](#). Roll-over subjects who did not complete the BPI at EOS/Day 169 will complete this assessment at the screening visit.

### **6.13 Concomitant Medication Assessments**

The Investigator or designee will record any concomitant therapies given for 30 days prior to the start of and during the course of the study on the concomitant medication page of the subject's source documentation and eCRF. Any changes in concomitant therapy during the study will also be documented, including cessation of therapy, initiation of therapy, and dose changes.

### **6.14 Removal of Subjects from the Study**

Subjects will be free to withdraw at any time for any reason, or they may be withdrawn if necessary, to protect their health and safety or the integrity of the study data.

The Investigator or medically qualified sub-investigator may choose to withdraw a subject from the study at any time. Reasons for removing a subject from the study may include, but are not limited to the following:

- Protocol deviation that might compromise data integrity, protocol compliance, or subject safety,
- An AE is reported that compromises or potentially compromises subject safety,
- The Sponsor or Investigator terminates the study, or
- The subject requests to be discontinued from the study (i.e., subject declines further study participation).

If a subject withdraws prematurely from the study after receiving IMP, the primary reason for withdrawal will be documented as 1 of the above, lost to follow-up, or other in the source documentation.



In the event a subject is lost to follow up, the site staff must make reasonable attempts to contact the subject. A minimum of 2 documented telephone calls followed by a certified mailed letter is considered reasonable.

#### 6.14.1 Early Removal of RBP-6000

In the event of an emergency or if a subject withdraws or is withdrawn within the first 14 days of receiving an injection of RBP-6000, subjects may have the option to have the depot surgically removed by a physician delegated to perform surgery. The medically responsible physician should carefully discuss this option with subjects given the use of ATRIGEL Delivery System and the feasibility of extracting the depot. The surgical procedure requires a small incision in the abdomen where the depot was placed, removal of the depot with forceps, and suturing to close the incision. The subject should have the EOS assessments performed at the time of early removal of RBP-6000. Subjects that have had an RBP-6000 depot removed should have follow-up telephone contact(s) within 7 to 14 days to assess status and for resolution of related AEs. In the event a subject cannot be contacted for the follow-up telephone contact, a minimum of 2 documented telephone calls followed by a certified mailed letter is considered reasonable. At this point, the subject may be considered lost to follow-up.

The extracted RBP-6000 depot will be disposed of into an appropriate, secure biohazard container per the standard operating procedures (SOPs) at the study site.

Detailed RBP-6000 depot removal instructions are in [Appendix 8](#).

#### 6.14.2 Stopping Rules

The Investigator must contact the Sponsor immediately to discuss whether to suspend dosing if an AE or laboratory abnormalities indicates that continued dosing of subsequent subjects would not be tolerated or would jeopardize the subjects' safety. The Sponsor alone may suspend dosing at any time for any reason.

Factors that must be considered for suspension of dosing include the frequency, severity, clinical significance, possible causality, and anticipated reversibility of all observed AEs or laboratory abnormalities for each specific SC injection group. If dosing is suspended, the IRB will be notified in accordance with IRB requirements.

#### 6.14.3 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (i.e., the subject signs the ICF) but who did not receive study medication.

Rescreening of a *de novo* subject may be permitted after consultation with the study medical monitor.



## 6.15 Other Study Procedures

### 6.15.1 Counseling/Behavioral Therapy

After enrollment, subjects will receive manual-guided, individual behavioral therapy once a week for 5 weeks, then bi-weekly (every 2 weeks) up until injection 6, at which point it will occur monthly to accompany the pharmacotherapy as indicated in the SOEs ([Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#)). Behavioral therapy will continue through the end of the study (EOS/ET visit). It is at the Investigator's discretion to provide additional behavioral counseling above this standard frequency. The reason(s) that additional counseling was provided should be documented in source documentation. Behavioral therapy can be conducted by any appropriately trained staff member at the site.

An Individual Drug Counseling (IDC) reference manual will be provided to each site.

### 6.15.2 Unscheduled Visits

If unscheduled visits occur, the Investigator must record the following in the subject's source documentation:

- Any AEs
- Reason for unscheduled visit
- Recording of any changes or additions to concomitant medications dose or regimen
- COWS (if deemed appropriate)
- Any clinical assessments deemed appropriate for the clinical care of the subject

Unscheduled visits should not alter the timing of the routine study schedule.

### 6.15.3 Additional Care of Study Subjects Following Completion of the Study

Each subject will be evaluated on his or her final study day. Subjects who experience SAEs at the EOS, or experience the onset of an SAE after the final visit, will be followed up as described in Section [6.10.11](#). No other additional care of study subjects will take place following completion of the study.

### 6.15.4 Treating Toxicity

Treatment of suspected RBP-6000 toxicity should be at the judgment of the Investigator or medically-qualified sub-investigator and may include an attempt to remove the depot if toxicity is discovered within the first 14 days post injection. Subjects who have had RBP-6000 removed will be followed up according to the procedures described in the SOE (EOS/ET Visit; [Appendix 3](#) and [Appendix 5](#)) and Section [6.14](#).

### 6.15.5 Ancillary Medications

Treatment of signs and symptoms of opioid withdrawal after enrollment can be treated with ancillary medications allowed by the protocol, as clinically indicated by the Investigator or

physician Sub-Investigator. Subjects whose symptoms are not manageable will be discontinued from the study and will be followed up according to the procedures described in the SOE (EOS/ET Visit; [Appendix 3](#) and [Appendix 5](#)) and Section 6.14.

## **6.16 Appropriateness of Measurements**

Within the study population of opioid-dependent subjects, certain common signs and symptoms are displayed that must be evaluated for safety and efficacy of treatment during clinical trials. The instruments used (e.g., COWS, SOWS, Opioid Craving VAS, and eC-SSRS) were developed to measure the specific symptoms exhibited by and challenges facing opioid-dependent individuals.

## 7 STUDY ACTIVITIES

This study will be conducted as a fully non-residential (outpatient) study. An overview of the study is shown in [Figure 2](#) and [Figure 3](#). Details on procedures/activities for this study are provided in [Section 6](#) and SOEs are provided in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#).

## **8 QUALITY CONTROL AND ASSURANCE**

### **8.1 Quality Control**

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigators and associated personnel before the study, periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory into the Sponsor's (or designee's) database. Written instructions will be provided for study drug preparation and dosing, collection, preparation, and shipment of blood, plasma, and urine samples. Guidelines for eCRF completion will be provided and reviewed with study personnel before the start of the study. The Sponsor (or designee) will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor (or designee). Any discrepancies will be resolved with the Investigator or suitably qualified designee, as appropriate.

### **8.2 Quality Assurance**

This study will be organized, performed, and reported in compliance with the protocol, Standard Operating Procedures (SOPs), working practice documents, and applicable regulations and guidelines.

In accordance with the standards defined in Sponsor SOPs and applicable regulatory requirements, clinical studies sponsored by Sponsor are subject to Sponsor Quality Audits at the study sites that will be conducted by personnel from an appropriate unit. Site audits will be made periodically by the Sponsor's (or contractor's) qualified compliance auditing team, which is an independent function from the study conduct team. Audits will include review of, but are not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner. Full consultation with the Investigator will be made prior to and during such an audit, which will be conducted according to the Quality Assurance Unit SOPs. In addition, this study is subject to inspection by regulatory authorities. If such a regulatory inspection occurs, the Investigator agrees to allow the regulatory inspector direct access to all relevant study documents. The investigator should contact the Sponsor immediately if this occurs and must fully cooperate with the inspection conducted at a reasonable time in a reasonable manner.

## 9 PLANNED STATISTICAL METHODS

### 9.1 General Considerations

A Statistical Analysis Plan (SAP) will be prepared after the protocol is approved and before database lock occurs. The SAP will provide further details regarding the definition of analysis endpoints, data handling rules, and the statistical methodology to be used to address all study objectives. The SAP will also include formats for the summary and analysis tables, listings, and graphical displays.

This section describes methods for sample size determination, analysis populations, and planned analyses for, safety, PK, and clinical outcomes endpoints. Additional unplanned analyses may be required after all planned analyses have been completed. Any unplanned analyses will be clearly identified in the clinical study report. Any deviations from the analyses described below will be included in the SAP, which will form Appendix 16.1.9 of the clinical study report.

Continuous variables will be summarized using descriptive statistics such as means, standard deviations (SD), medians, minimums, and maximums. Categorical variables will be reported as frequency counts (including number missing) and the percentage of subjects in corresponding categories. Individual subject data will be presented by subject in data listings. Data listings will include all data collected from the initial screening visit to the end of study for all subjects enrolled.

### 9.2 Determination of Sample Size

There is no formal sample size calculation. Approximately 300 *de novo* subjects as well as approximately 300 subjects who completed the RB-US-13-0001 efficacy study will be enrolled into this study to ensure at least 100 subjects reach 1 year of treatment with RBP-6000.

### 9.3 Analysis Populations

The following populations will be used for data analyses:

#### 9.3.1 Safety Population

The Safety Population comprises all subjects who received at least 1 dose of RBP-6000 during the open-label treatment phase of the study. This population will be used for all safety analyses.

#### 9.3.2 Clinical Outcome Assessment and PK Populations

The Clinical Outcome Assessment population will include subjects who were dosed with RBP-6000 and have at least 1 post-dose Clinical Outcome Assessment value.

The PK Population will include any subject who receives a dose of RBP-6000 or at least 1 dose of SUBOXONE sublingual film and has at least 1 sample collected post-dose.

## 9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics (gender, race, age, weight, height) will be summarized by treatment group using descriptive statistics. Qualitative variables (gender, race) will be summarized using frequencies while quantitative variables (age, weight, height) will be summarized using mean, SD, median, minimum, and maximum.

## 9.5 Primary Analysis

### 9.5.1 Safety Endpoints

Safety variables will include AEs, local injection site tolerability (e.g., injection site grading); injection site pain using a subject-reported VAS; suicidality using the eC-SSRS, concomitant medications; changes in clinical laboratory results (hematology, chemistry and urinalysis); vital sign measurements; 12-lead ECGs, physical examination results; body weight, height, BMI, and abdominal fat measurement (waist-to-hip ratio). Safety variables will be analyzed using the safety population.

Baseline is defined as the last non-missing value prior to SC injection on Day 1. No imputation of missing values will be performed.

#### 9.5.1.1 Adverse Events

All AEs will be coded using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) and reported to the FDA. AEs that began more than 30 days after the last study subject assessment day will not be included in the safety analysis. Only TEAEs occurring post administration of RBP-6000 will be included in the safety analysis (See [Section 6.10.10](#)).

The incidence of AEs (number and percent of subjects reporting the AE at least once during the study) will be summarized for all AEs, by the relationship to study drug and by severity.

#### 9.5.1.2 Laboratory Data

At each visit where clinical laboratory assessments are conducted, summary statistics for the absolute laboratory value and the changes from baseline will be presented.

#### 9.5.1.3 Vital Signs

Vital signs measurements will be assessed for clinical relevance and be performed as deemed medically necessary by research personnel. Vital signs will be taken after the subject has completed a minimum 3-minute rest in the supine position. Systolic and diastolic BP measurements will be assessed while supine throughout the trial.

#### 9.5.1.4 Other Variables Related to Safety

Results from 12-lead ECGs will be categorized as normal, abnormal clinically significant, or abnormal not clinically significant and will be summarized by time point using frequency counts

and percentages. ECG interval measurements as well as change from baseline will also be summarized by time point using descriptive statistics (mean, median, SD, minimum, maximum). Additional analysis of ECG parameters will be outlined in the SAP.

Medical history will be coded using MedDRA and summarized by treatment group as described for AEs ([Section 9.5.1.1](#)). Body weight, height, BMI, and abdominal fat measurement (waist-to-hip ratio) will be summarized using descriptive statistics (mean, median, SD, minimum, maximum), including change from baseline.

Total eC-SSRS scores will be summarized using descriptive statistics (mean, median, SD, minimum, maximum), including change from baseline. Subjects' self-reported illicit drug use from the TLFB will be summarized as descriptive statistics.

Prior and concomitant medications will be coded using the most recent version of the World Health Organization (WHO) Drug dictionary. Incidence (number and percent of subjects reporting the medication at least once during the study) will be summarized for all concomitant medications.

Local injection site tolerability as assessed by the Injection Site Grading scale will be summarized by category and severity using frequency counts and percentages similar to summaries for AEs ([Section 9.5.1.1](#)). Injection Site Pain VAS scores will be summarized by dose, injection, and time point after injection. The burning/stinging categorical variable (Yes/No) will be summarized by percent of responses in each treatment.

## 9.6 Secondary Analysis

### 9.6.1 Clinical Outcomes Assessments

COWS, SOWS and Opioid Craving VAS total scores will be summarized using descriptive statistics (mean, median, SD, minimum, maximum), including change from baseline. Subjects' self-reported illicit drug use from the TLFB will be summarized using descriptive statistics.

The cumulative distribution function (CDF) of the percentage of urine samples negative for opioids and that of the percentage of self-reports from the TLFB negative for illicit opioid use will be calculated. Other outcome efficacy measures will be estimated using descriptive statistics.

## 9.7 Other Analyses

### 9.7.1 PK/PD Modeling

The population PK model established using the data collected in the double-blind, placebo-controlled, efficacy study (Study RB-US-13-0001) will be refined using the PK samples collected in the present study to characterize the disposition of buprenorphine and norbuprenorphine following SC injections of RBP-6000, with the assessment of potential covariates affecting the PK of both compounds. Subsequently, the relationships between buprenorphine plasma concentrations and clinical outcomes assessments will be investigated.

These relationships will be initially assessed in a descriptive manner, and, if applicable, appropriate PK/PD models will be developed to describe these relationships. A stand-alone modeling analysis plan will be generated, and the results will be reported in a standalone modeling report.

### 9.7.2 Health Economic and Outcomes Assessment

The health economic and outcomes research endpoints for this study are:

- EQ-5D-5L
- SF-36v2
- MSQ
- HCRU
- TEA
- ASI Lite
- BDI-II
- BPI

Summary scores for these measures will be calculated, as appropriate. Categorical variables will be summarized using frequencies and percentages. Continuous measures will be summarized using descriptive statistics (mean, standard deviation, median, minimum, maximum) as appropriate. An analysis of change will be conducted. A stand-alone statistical analysis plan will be developed prior to database lock for health economics and outcomes research assessments.

A separate stand-alone SAP will be developed prior to database lock with full detail regarding health economics and outcomes analyses.

## 9.8 Handling of Missing Data

For dichotomous outcome measures such as UDS results (negative; non-negative) and self-reports for illicit opioid use (negative; non-negative), any missing observation will be recorded as “non-negative.” For all continuous endpoints (e.g., COWS, SOWS, and VAS), the missing data mechanism will be assumed to be either missing completely at random (MCAR) or missing at random (MAR). The missing data will not be imputed because the analysis method, mixed model for repeated measures (MMRM), does not require any imputation and no sensitivity analyses will be performed on these variables. For time-to-event variables, if the event of interest is not observed prior to withdrawal or end of treatment, the observations will be censored at the time of withdrawal or at the end of treatment. For example, if some subjects still have not had a urine sample negative for opioids combined with self-reports negative for illicit opioid use when the study ends or at the time of withdrawal from the study, then the time to first urine sample negative for opioids combined with self-reports negative for illicit opioid use will be censored at the last time they were assessed.



## **9.9 Subjects Who Withdraw from the Study**

Subjects who withdraw after receiving RBP-6000 will not be replaced.

## **9.10 Interim Analyses**

An Interim analysis will be performed once at least 100 subjects have completed the study.

## **10 ADMINISTRATIVE CONSIDERATIONS**

### **10.1 Investigators and Study Administrative Structure**

#### **10.1.1 Indivior Inc.**

Indivior Inc.  
10710 Midlothian Turnpike, Suite 430  
Richmond, VA 23235

#### **10.1.2 Investigational Site(s)**

This study will be conducted at up to 50 sites in the US.

#### **10.1.3 Laboratories**

The safety laboratory tests (serum chemistry, hematology, serology, and urinalysis), as well as the specialty laboratory tests (Bioanalytical and Pharmacokinetic) will be conducted at a central laboratory that is certified and accredited to perform the assigned assessments.

Collection of safety laboratory samples is described in Section 6.6.2. The Clinical Laboratory will provide normal ranges and collection, processing, and shipping instructions to the sites in a separate laboratory reference manual.

### **10.2 Institutional Review Board or Independent Ethics Committee Approval**

The protocol will be reviewed by an independent, appropriately constituted, centralized IRB/Independent Ethics Committee (IEC). Study enrolment and protocol related procedures, which do not form part of the subject's normal clinical treatment, will not be performed until the IRB/IEC of record has provided written approval of the protocol or a modification thereof. The IRB/IEC must be constituted and operate in accordance with the principles and requirements of ICH GCP.

Study drug can only be supplied to the Investigator after documentation on all ethical and legal requirements for starting the study has been received by the Sponsor. This documentation must also include an IRB/IEC membership list that contains member's occupations. If the IRB/IEC will not disclose the names of the committee members, the IRB/IEC Federalwide Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/IEC should mention the study title, study code, study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member.

### **10.3 Ethical Conduct of the Study**

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH GCP guidelines, and applicable regulatory and country-specific

requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides the public assurance that the rights, safety, and well-being of study subjects are protected and that the clinical study data are credible.

## **10.4 Subject Information and Consent**

Prior to the subject incurring the first study related procedure, the Investigator or designated individual will explain to each subject the nature of the study, its purpose, procedures, expected duration, alternative therapies available, and the benefits and risks involved in study participation. It should also be mentioned that all informed consent documents and other documents used in the conduct of the study have been approved by an IRB/IEC.

In the case of a non-medically qualified person conducting the consent process, he/she should have ready access to a medically qualified investigator to whom any questions from the study subject may be referred. Subjects will be given consent documents to review and the opportunity to ask questions. Subjects must be informed of their right to withdraw from the study at any time without prejudice.

After this explanation and before any study-specific procedures have been performed, the subject must voluntarily sign and date the ICF to indicate he/she wishes to participate in study. The Investigator or the individual designated to conduct the consent discussion for the Investigator must also sign and date the ICF. The time (hour and minute) the consent is signed must also be recorded in the subject's source notes, by the person obtaining consent from the subject. Verbal informed consent followed by a signed consent short form is not acceptable to Sponsor.

Prior to participation in the study, the subject will receive a copy of the signed and dated ICF along with an emergency card with contact information for the Investigator and site staff in the event of a medical emergency during the study.

## **10.5 Subject Confidentiality**

All subject-identifying documentation generated in this study must be considered confidential and must not be disclosed to any persons not directly concerned with the study without written permission from the subject. However, authorized regulatory officials and Sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol and the informed consent signed by the subject, unless otherwise agreed to in writing by the Sponsor.

Each subject will be identified by initials and an assigned subject number when reporting study information to any entity outside of the study center. Data containing subject identification will not be removed from the study center without subject identifiers having been redacted.

## 10.6 Study Monitoring

In accordance with applicable regulations, GCP, and Sponsor procedures, the clinical monitor(s) will periodically contact the site, including conducting on-site visits at intervals agreed by the Investigator and documented in the Clinical Monitoring Plan and the Site Initiation Visit Report.

The clinical monitor(s) will contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel. In accordance with applicable regulations and GCP guidelines, the Investigator shall make available for direct access all study-related records upon request of the Sponsor, the Sponsor's agents, clinical monitor(s), auditors, and/or IRB/IEC. The Sponsor's monitors will visit the site during the study in addition to maintaining frequent telephone and written communication. The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrolment rate.

The Investigator must allow the clinical monitor(s) direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the clinical monitor(s) to discuss findings and any relevant issues.

### 10.6.1 Study and Site Closure

Upon completion of the study, study closeout activities must be conducted by the Sponsor or its designee in conjunction with the Investigator, as appropriate.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the Sponsor will discuss this with the Investigator (including the reason[s] for taking such action) at that time. The Sponsor will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator must inform the IRB/IEC promptly and provide the reason(s) for the suspension or termination. If the study is prematurely discontinued, all study data and study drug remaining on site must be returned to the Sponsor or its designee.

## 10.7 Case Report Forms and Study Records

The Investigator is responsible for the quality of the data recorded in the electronic Case Report Forms (eCRFs). The data recorded should be a complete and accurate account of the subject's record collected during the study. Study data are not to be gathered directly onto the eCRF but must be gathered onto primary source documents at the study site. Completion of source documents will precede the completion of the eCRF. Source data transfer into the eCRF should occur timely and on an ongoing basis. Source documents may be electronic, hard copy, or a combination of both. Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the investigators and made available for direct inspection by the authorized study personnel outlined in the ICF. The ePRO

tablet will be considered the source document for individual ePRO elements such as study-specific scales when collected directly onto the tablet.

Data collection will be completed according to the guidelines provided by Sponsor or its designee.

For all subjects who signed an informed consent, all required data are to be recorded using source documents and reported on the eCRF, except for study scales that are recorded directly on the ePRO tablet. Site staff will receive training on the eCRF completion guidelines and requirements for source documentation.

Completed eCRFs will be reviewed by the study monitor in line with eCRF completion guidelines for the study to ensure completeness and consistency. The study monitor will review every subject's eCRF with source data verification for at least all critical data points. The clinical management plan for this study will define the level of source data verification required for non-critical data points. Any discrepancies found during the eCRF review will be clarified by the Investigator or designated individual. This includes eCRF reviews at the site by Sponsor or its designee, or during quality assurance review of the data.

An explanation must be documented for any missing data. Any changes to information in the study progress notes and other source documents will be initialled and dated on the day the change is made by a site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (e.g., ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

The Investigator must sign and date a declaration attesting to his/her responsibility for the quality of all data recorded, and that the data represents a complete and accurate record of each subject's participation in the study.

All eCRF entries, corrections, and alterations must be made by the Investigator or designated individual. The Investigator or designated individual must adjust the eCRF (if applicable) and complete the query.

## **10.8 Data Monitoring Committee**

Not applicable; there will be no data monitoring committee for this study.

## **10.9 Protocol Deviations**

This study is intended to be conducted as described in this protocol. At the outset of the study, a process for defining and handling protocol deviations will be established and defined in the medical management plan. This will include determining which violations will be designated important and require immediate notification to the Sponsor. In the event of a deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designated individual must contact the Sponsor at the earliest possible time by telephone. This will allow an early joint

decision regarding the subject's continuation in the study. This decision will be documented by the Investigator and the Sponsor, and reviewed by the monitor. Deviations from the protocol are to be documented. The Investigator or designated individual will be responsible for identifying and reporting all deviations, which are defined as isolated occurrences involving a procedure that did not follow the study protocol or study-specific procedure. Deviations will be reported as required to the IRB and in the final study report.

## **10.10 Access to Source Documentation**

The Investigator must agree to complete a subject identification and enrolment log to permit easy identification of each subject during and after the study. This document will be reviewed by the Sponsor site contact for completeness. The subject identification and enrollment log will be treated as confidential and will be filed by the Investigator in the investigator site file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by initials and assigned number only. The Investigator must also complete a subject-screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs; concomitant medications; study drug administered; date of study completion or early discontinuation, and reason for early discontinuation if applicable.

## **10.11 Data Generation and Analysis**

### **10.11.1 Data Collection and Data Management**

Study specific data that has been outlined in the protocol will be entered into the clinical database by individual(s) designated by the Investigator in accordance with the CRF Completion Guidelines. Data is verified electronically using a series of on-line programmed edit checks that have been created by the Clinical Data Manager and programmed by the Clinical Data Programmer or Designee. Data discrepancies will be brought to the attention of the clinical team and investigated by the CRA and Site Study Coordinator. CRAs will review and verify all data collected in the eCRF against source documentation during scheduled monitoring visits. The CRA will work closely with the Site Study Coordinator to address any discrepancies which have been found so that proper resolutions can be made and documented into the clinical database. An audit trail within the system will track all changes made to the data.

### **10.11.2 Database Quality Assurance**

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the investigational site. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

## **10.12 Retention of Data**

All documents pertaining to the study, including all versions of the approved study protocol, copy of the informed consent document and Health Insurance Portability and Accountability Act documents, completed eCRFs, source documents (subject records, subject diaries, hospital records, laboratory records, drug accountability records, etc.), and other study-related documents will be retained in the permanent archives of the study site.

The Investigator must therefore notify and obtain approval in writing from the Sponsor prior to destruction of any study records or provide an opportunity for the Sponsor to collect such records. If the investigator withdraws from the study (e.g., relocation, retirement) all study-related records should be transferred, in a written agreement with the Sponsor, to a mutually agreed upon designee within a Sponsor-specified timeframe.

## **10.13 Financial Disclosure**

Indivior requires, for each study, the disclosure of any financial interests from each investigator or sub-investigator, including financial interests of the spouse and each dependent child of the investigator who is directly involved in the treatment or evaluation of research subjects that could affect the reliability of data submitted to regulatory authorities. The collection of this financial interest information at the start of the study, as well as any updates should this information change, is required by the FDA when submitting a marketing application and is in line with the GCP requirement to consider any potential conflicts of interest.

## **10.14 Publication and Disclosure Policy**

A clinical study report will be prepared following completion of the study. The report will be a record of the total study conduct and will be subject to Sponsor approval and restrictions on distribution/disclosure.

The study data will be owned by the Sponsor. Publication of any and all data will be at the discretion of the Sponsor. The Investigator will not disseminate, present, or publish any of the study data without the prior written Sponsor approval to do so.

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## Appendix 1 Schedule of Events – Screening and SUBOXONE Film Induction

Evaluation	Screening Visit (Up to 3 days after EOS Visit/Day 169 of RB-US-13-0001 for roll-over subjects) <sup>15</sup>	SUBOXONE sublingual film Run-In						
		Induction (3 days)			Dose Adjustment (1 to 11 days)			
	Days -21 to -15	Day -14	Day -13	Day -12	Day -11	Day -8	Day -4	Day -1
						+1 day	±1 day	-1 day
Informed Consent	X							
Inclusion/Exclusion Criteria Reviewed	X							
IWRS	X	X	X	X	X	X	X	X
Demographics <sup>1</sup>	X							
Medical History <sup>1</sup>	X							
eC-SSRS (Baseline Version)	X <sup>13</sup>							
Physical Examination <sup>2</sup>	X <sup>13</sup>							
Vital Signs <sup>3</sup>	X <sup>13</sup>	X	X	X	X	X	X	X
Body Weight	X <sup>13</sup>							
BMI Calculation	X <sup>13</sup>							
Hip-to-Waist Ratio	X <sup>13</sup>							
12-lead ECG (supine > 10 min) <sup>4</sup>	X <sup>13</sup>							
Urine Drug Screen (UDS)	X <sup>13</sup>							
Urine Pregnancy Test <sup>5</sup>		X						
Screening Labs / Hormone Panel	X <sup>13</sup>							
Urinalysis/ Hematology/Serum Chemistry	X <sup>13</sup>							
Opioid Craving VAS <sup>6</sup>	X <sup>13</sup>				X	X	X	X
Clinical Opiate Withdrawal Scale (COWS) <sup>6</sup>	X <sup>13</sup>	X	X	X	X	X	X	X
Subjective Opiate Withdrawal Scale (SOWS) <sup>6</sup>	X <sup>13</sup>	X	X	X	X	X	X	X

Evaluation	Screening Visit (Up to 3 days after EOS Visit/Day 169 of RB-US-13-0001 for roll-over subjects) <sup>15</sup>	SUBOXONE sublingual film Run-In						
		Induction (3 days)			Dose Adjustment (1 to 11 days)			
	Days -21 to -15	Day -14	Day -13	Day -12	Day -11	Day -8	Day -4	Day -1
						+1 day	±1 day	-1 day
BDI-II	X <sup>13,14</sup>							
BPI	X <sup>13, 14</sup>							
TLFB Interview	X <sup>13</sup>							
Concomitant Medications	X <sup>7, 13</sup>	X	X	X	X	X	X	X
AE Assessment <sup>8</sup>	X <sup>13</sup>	X	X	X	X	X	X	X
Day -1 Criteria Reviewed					X <sup>9</sup>	X <sup>9</sup>	X <sup>9</sup>	X <sup>10</sup>
SUBOXONE SL film administration <sup>11</sup>		X	X <sup>16</sup>	X <sup>16</sup>	X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>	X <sup>12</sup>
EQ-5D-5L	X <sup>13</sup>							
SF-36v2	X <sup>13</sup>							
Health Insurance	X <sup>13</sup>							
HCRU	X <sup>13</sup>							
TEA	X							

AE = adverse event; BDI-II = Beck Depression Inventory II; BMI = body mass index; BPI = Brief Pain Inventory Short Form; COWS = Clinical Opiate Withdrawal Scale; eC-SSRS = electronic Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D-5L = EuroQol EQ-5D-5L;; HCRU = Healthcare resource utilization; IXRS=Interactive voice/web response system; MSQ = Medication Satisfaction Questionnaire; SF-36v2 = 36-Item Short Form Health Survey, Version 2; SL = sublingual; SOWS = subjective opiate withdrawal scale; TEA = Treatment Effectiveness Assessment; TLFB = Timeline Followback; VAS = Visual Analog Scale

1. A complete medical and psychiatric history, including use of tobacco, drugs of abuse, alcohol and caffeine. Update demographics for roll-over subjects.
2. Complete examination (excluding pelvic, breast, and rectal), including general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities, and a brief neurological assessment.
3. Includes blood pressure (BP; supine ≥ 3 minutes), pulse oximetry, pulse rate, respiratory rate, oral temperature, and height (screening visit only). Vital signs will be assessed within ≤60 minutes before administration of SUBOXONE sublingual film.

- 
4. Must be performed prior to labs
  5. Only for female subjects who are of childbearing potential (not postmenopausal or surgically sterile for at least 1 year).
  6. Assessments should be performed prior to each SUBOXONE SL film dosing and at approximately the same time each day ( $\pm 2$  hours).
  7. Include a review of previous (within 30 days prior to screen) and ongoing medications.
  8. A PK sample will be taken as soon as possible after any SAE is reported. If possible, an additional sample should be collected when the SAE has been resolved.
  9. This visit becomes Day -1 if the following criteria are met:
    - No allergic reaction to SUBOXONE sublingual film
    - Daily dose of SUBOXONE sublingual film between 8 mg/2 mg - 24 mg/6 mg (inclusive) buprenorphine/naloxone.
    - COWS score of  $\leq 12$
    - Opioid Craving VAS score of  $\leq 20$  mmIf Day -1 criteria are met, the subject will be scheduled the following day (Injection Visit 1/Day 1) to receive the first injection of RBP-6000 after enrollment criteria are met.
  10. If Day -1 criteria are not met after 14 days of SUBOXONE sublingual film treatment, and a subject still has significant withdrawal signs/symptoms and opioid cravings (COWS score  $>12$  and Opioid Craving VAS  $>20$  mm), they will not be eligible to continue in the study. They will be provided with information on the options for opioid use disorder treatment.
  11. SUBOXONE SL film dosing should take place at the same time of day ( $\pm 2$  hours).
  12. Subjects should **not** take their dose of SUBOXONE SL film until after it has been determined if they have met Day -1 criteria (footnote #10).
  13. RB-US-13-0001 roll-over subjects study procedures completed at EOS/Day 169 will serve as the screening assessments for Protocol RB-US-13-0003
  14. Roll-over subjects who did not complete the BDI-II and the BPI at EOS/Day 169 visit will complete these assessments at Screening for Protocol RB-US-13-0003 **only after** consent for the RB-US-13-0003 is obtained.
  15. For roll-over subjects only and at the Investigator's discretion: Induction can begin on the day of screening for subjects who meet study criteria.
  16. Subjects with a score for COWS of  $>12$ , or subjects reporting opioid withdrawal signs/symptoms overnight, may receive a dose of an additional 4 mg. If the COWS score is still  $>12$  one hour later, another 4 mg dose can be given. Subjects should not exceed a maximum dose of 16 mg/4 mg for Induction Day 2, or 24 mg/6 mg on subsequent days.

## Appendix 2 Schedule of Events – RBP-6000 Injection 1 – 3 Visits

Evaluation	Inj 1	Post Inj 1 Assessments					Inj 2	Post Inj 2 24hrs	Post Inj 2	Inj 3	Post Inj 3 24hrs	Post Inj 3
	Wk1 D 1	Wk1 D 2	Wk2 D 8	Wk3 D 15	Wk4 D 22	Wk5 D 29	Wk5 D 30	Wk5 D 30	Wk7 D 43	Wk9 D 57	Wk9 D 58	W11 D 71
Window		+1	±2	±2	±2	-2/ +4	+1	±4	-2/ +4	+1	-2/ +4	
IWRS	X					X			X			
Enrollment	X											
Vital Signs <sup>1</sup>	X	X	X	X	X	X		X	X			X
Body Weight	X											
BMI Calculation	X											
Hip-to-Waist Ratio	X											
12-lead ECG <sup>2</sup> (supine ≥ 10 min)	X	X	X	X	X	X		X	X			X
Hematology/ Serum Chemistry <sup>3</sup>	X			X		X		X	X			X
Hormone Panel <sup>3</sup>	X											
Urinalysis <sup>3</sup>	X			X		X		X	X			X
Urine Pregnancy Test <sup>4</sup>	X			X		X		X	X			X
Urine Drug Screen <sup>5</sup>	X	X	X	X	X	X		X	X			X
PK Sampling (Roll-over patients only) <sup>6</sup>	X			X		X		X	X			X
Concomitant Medications	X	X	X	X	X	X	X <sup>13</sup>	X	X	X <sup>13</sup>		X
AE Assessment <sup>7</sup>	X	X	X	X	X	X	X <sup>13</sup>	X	X	X <sup>13</sup>		X
eC-SSRS (Since last-visit-version) <sup>7</sup>	X		X	X	X	X		X	X			X
TLFB Interview <sup>7</sup>	X		X	X	X	X		X	X			X
Opioid Craving VAS <sup>7</sup>	X	X	X	X	X	X		X	X			X
COWS <sup>7</sup>	X	X	X	X	X	X		X	X			X
SOWS <sup>7</sup>	X	X	X	X	X	X		X	X			X
BDI-II <sup>7</sup>	X					X			X			
BPI <sup>7</sup>	X					X			X			
RBP-6000 Injection	X					X			X			
Injection Site Grading Scale <sup>8</sup>	X	X				X			X			
Injection Site Pain VAS <sup>9</sup>	X					X			X			

Evaluation	Inj 1	Post Inj 1 Assessments				Inj 2	Post Inj 2 24hrs	Post Inj 2	Inj 3	Post Inj 3 24hrs	Post Inj 3
	Wk1 D 1	Wk1 D 2	Wk2 D 8	Wk3 D 15	Wk4 D 22	Wk5 D 29	Wk5 D 30	Wk7 D 43	Wk9 D 57	Wk9 D 58	W11 D 71
Window		+1	±2	±2	±2	-2/ +4	+1	±4	-2/ +4	+1	-2/ +4
Injection Site Evaluation <sup>10</sup>	X	X	X	X	X	X		X	X		X
Behavioral Therapy <sup>11</sup>	X		X	X	X	X		X	X		X
EQ-5D-5L <sup>7</sup>	X								X		
SF-36v2 <sup>7</sup>	X								X		
MSQ <sup>7</sup>									X		
Health Insurance	X					X			X		
HCRU	X					X			X		
TEA	X					X			X		
ASI Lite	X								X <sup>12</sup>		

AE = adverse event; ASI = Addiction Severity Index; BDI-II = Beck Depression Inventory II; BMI = body mass index; BPI = Brief Pain Inventory Short Form; COWS = Clinical Opiate Withdrawal Scale; eC-SSRS = electronic Columbia Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; EQ-5D-5L = EuroQol EQ-5D-5L; HCRU = Healthcare resource utilization; Inj. = injection; IXRS=Interactive voice/web response system; MSQ = Medication Satisfaction Questionnaire; PK = pharmacokinetic/pharmacokinetics; SF-36v2 = 36-Item Short Form Health Survey, Version 2; SC = subcutaneous; SOWS = subjective opiate withdrawal scale; TEA = Treatment Effectiveness Assessment; TLFB = Timeline Followback; VAS = Visual Analog Scale

1. Includes blood pressure, pulse oximetry, pulse rate, respiratory rate, and oral temperature which must be taken after subject is supine  $\geq 3$  minutes. On injection day 1, vital signs will be taken  $\leq 60$  minutes prior to SC injection, and then 0.5 ( $\pm 15$  minutes), and 2 hours post SC injection ( $\pm 15$  minutes). For all subsequent injection days, vital signs will be taken  $\leq 60$  minutes prior to SC injection, and 1 hour post SC injection ( $\pm 15$  minutes). For non-injection days, vital signs will be taken at approximately the same time of day as the Day 1 pre-injection vital signs.
2. On Injection day 1, an ECG will be performed  $\leq 60$  minutes prior to SC injection, and then 0.5 ( $\pm 15$  minutes), and 2 hours post SC injection ( $\pm 30$  minutes). For all subsequent injection days, an ECG will be recorded  $\leq 60$  minutes prior to SC injection, and 1 hour post SC injection ( $\pm 30$  minutes). For non-injection days, an ECG will be performed at approximately the same time of day as the Day 1 pre-injection ECG. All ECGs must be performed prior to laboratory assessments.
3. On injection days blood and urine samples will be taken  $\leq 60$  minutes prior to SC injection and after the ECG has been performed.
4. Only for female subjects who are of childbearing potential (not postmenopausal or surgically sterile for at least 1 year).
5. An additional urine drug screen can be done if use is suspected. Oxycodone may not show up in all opiate assays and should be assessed separately.
6. PK samples taken for roll-over subjects only. See PK table (Appendix 6) for exact time points. However, a PK sample should be taken as soon as possible after any SAE is reported regardless if the patient is *de novo* or roll-over. If possible, an additional sample should be collected when the SAE has been resolved.
7. Assessments should be performed prior to RBP-6000 injection and at approximately the same time each day  $\pm 2$  hours.



8. Local injection site grading will be performed at time of SC injection (within 10 minutes), 1 hour ( $\pm$  15 minutes). For Injection 1 only, the local injection site grading will also be taken 24 hours ( $\pm$  4 hours) post SC injection.
9. Injection Site Pain VAS will be completed by the subject within 1 minute after the completion of the injection and then at 5, 10, 15, 30, and 60 minutes ( $\pm$  5 minutes) post-completion of injection.
10. Injection site will be evaluated for evidence of attempted removal.
11. Additional unscheduled visits for behavioral therapy may be added at the Investigator's discretion.
12. Collect information for the Employment/Support Status, Alcohol, Drug, Legal, Family/Social, and Psychological section only. Follow-up version of the questionnaire (only circled items, no lifetime recall).
13. Subjects should be contacted by telephone at 24 hrs ( $\pm$  4 hours) and will be assessed for AEs and any changes to Con Meds. Subjects are not required to return to the site unless the investigator deems it medically necessary.

### Appendix 3 Schedule of Events – RBP-6000 Injection 4 – 6 Visits for all Subjects and End of Study/Early Termination and Follow-Up Visits for Roll-over Subjects

Evaluation	Inj 4	Post Inj 4 24hrs	Post Inj 4	Inj 5	Post Inj 5 24hrs	Post Inj 5	Inj 6	Post Inj 6 24hrs	EOS/ET <sup>13</sup>	Safety Follow-Up <sup>20</sup>
	Wk13 D 85	Wk13 D 86	W15 D 99	Wk17 D 113	Wk17 D 114	Wk19 D 127	Wk21 D 141	Wk21 D 142	Wk25 D 169	Wk29 D 197
Window	-2/ +4	+1	±4	-2/ +4	+1	±4	-2/ +4	+1	-2/ +4	-2/ +4
IWRS	X			X			X		X <sup>14</sup>	
Vital Signs <sup>1</sup>	X		X	X		X	X		X	
Body Weight	X						X		X	
BMI Calculation	X						X		X	
Hip-to-Waist Ratio	X						X		X	
12-lead ECG (supine ≥ 10 min) <sup>2</sup>	X		X	X		X	X		X	
Hematology/ Serum Chemistry <sup>3</sup>	X		X	X		X	X		X	
Hormone Panel <sup>3</sup>	X						X		X	
Urinalysis <sup>3</sup>	X		X	X		X	X		X	
Urine Pregnancy Test <sup>3</sup>	X		X	X		X	X		X	
Serum Pregnancy Test <sup>4</sup>										
Urine Drug Screen <sup>5</sup>	X		X	X		X	X		X	
PK Sampling (Roll-over patients only) <sup>6</sup>	X		X	X		X	X		X	
Concomitant Medications	X	X <sup>19</sup>	X	X	X <sup>19</sup>	X	X	X <sup>19</sup>	X	X
AE Assessment <sup>8</sup>	X	X <sup>19</sup>	X	X	X <sup>19</sup>	X	X	X <sup>19</sup>	X	X
eC-SSRS (Since last-visit-version) <sup>8</sup>	X		X	X		X	X		X	
TLFB Interview <sup>8</sup>	X		X	X		X	X		X	
Opioid Craving VAS <sup>8</sup>	X		X	X		X	X		X	
COWS <sup>8</sup>	X		X	X		X	X		X	
SOWS <sup>8</sup>	X		X	X		X	X		X	

Evaluation	Inj 4	Post Inj 4 24hrs	Post Inj 4	Inj 5	Post Inj 5 24hrs	Post Inj 5	Inj 6	Post Inj 6 24hrs	EOS/ET <sup>13</sup>	Safety Follow-Up <sup>20</sup>
	Wk13 D 85	Wk13 D 86	W15 D 99	Wk17 D 113	Wk17 D 114	Wk19 D 127	Wk21 D 141	Wk21 D 142	Wk25 D 169	Wk29 D 197
Window	-2/ +4	+1	±4	-2/ +4	+1	±4	-2/ +4	+1	-2/ +4	-2/ +4
BDI-II <sup>8</sup>	X			X			X		X	
BPI <sup>8</sup>	X			X			X		X	
RBP-6000 Injection	X			X			X			
Injection Site Grading Scale <sup>9</sup>	X			X			X			
Injection Site Pain VAS <sup>10</sup>	X			X			X			
Injection Site Evaluation <sup>11</sup>	X		X	X		X	X		X	
Behavioral Therapy <sup>12</sup>	X		X	X		X	X		X	
EQ-5D-5L <sup>8</sup>							X		X	
SF-36v2 <sup>8</sup>							X		X	
MSQ <sup>8</sup>							X		X	
Health Insurance <sup>8</sup>	X			X			X		X	
HCRU <sup>8</sup>	X			X			X		X	
TEA <sup>8</sup>	X			X			X		X	
ASI Lite							X <sup>17</sup>		X <sup>18</sup>	
Physical Examination <sup>15</sup>									X	
Review of Treatment Options <sup>16</sup>				X			X		X	
Alternative Treatment Agreed <sup>16</sup>									X	

AE = adverse event; ASI = Addiction Severity Index; BDI-II = Beck Depression Inventory II; BMI = body mass index; BPI = Brief Pain Inventory Short Form; COWS = Clinical Opiate Withdrawal Scale; eC-SSRS = electronic Columbia Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; EOS/ET = End of Study/Early Termination; EQ-5D-5L = EuroQol EQ-5D-5L; HCRU = Healthcare resource utilization; Inj. = injection; IXRS=Interactive voice/web response system; MSQ = Medication Satisfaction Questionnaire; PK = pharmacokinetic/pharmacokinetics; SF-36v2 = 36-Item Short Form Health Survey, Version 2; SC = subcutaneous; SL = sublingual; SOWS = subjective opiate withdrawal scale; TEA = Treatment Effectiveness Assessment; TLFB = Timeline Followback; VAS = Visual Analog Scale.

1. Includes blood pressure, pulse oximetry, pulse rate, respiratory rate, and oral temperature which must be taken after subject is supine  $\geq 3$  minutes. On days injections 2-12 are given, vital signs will be taken  $\leq 60$  minutes prior to SC injection, and 1 hour post SC injection ( $\pm 15$  minutes). For non-injection days, vital signs will be taken at approximately the same time of day as the Day 1 pre-injection vital signs.

2. On days injections 2-12 are given, an ECG will be performed  $\leq 60$  minutes prior to SC injection, and 1 hour post SC injection ( $\pm 30$  minutes). For non-injection days, an ECG will be performed at approximately the same time of day as the Day 1 pre-injection ECG. All ECGs must be performed prior to labs and PK samples.
3. On injection days, blood and urine samples will be taken  $\leq 60$  minutes prior to SC injection and after the ECGs has been performed.
4. Only for female subjects who are of childbearing potential (not postmenopausal or surgically sterile for at least 1 year).
5. An additional urine drug screen can be done if use is suspected. Oxycodone may not show up in all opiate assays and should be assessed separately.
6. PK samples taken for roll-over subjects only. See PK table ([Appendix 6](#)) for exact time points. However, a PK sample should be taken as soon as possible after any SAE is reported regardless if the patient is de novo or roll-over. If possible, an additional sample should be collected when the SAE has been resolved.
7. A PK sample will be taken as soon as possible after any SAE is reported. If possible, an additional sample should be collected when the SAE has been resolved.
8. Assessments should be performed prior to RBP-6000 injection and at approximately the same time each day  $\pm 2$  hours.
9. Local injection site grading will be performed at time of SC injection (within 10 minutes) and 1 hour ( $\pm 15$  minutes.)
10. Injection Site Pain VAS will be completed by the subject within 1 minute after completion of the injection and then at 5, 10, 15, 30, and 60 ( $\pm 5$  minutes) post-completion of injection.
11. Injection site will be evaluated for evidence of attempted removal.
12. Additional unscheduled visits for behavioral therapy may be added at the Investigator's discretion.
13. For roll-over subjects, the procedures at Week 25/Day 169 will serve as the EOS assessments. For *de novo* subjects who discontinued participation in the study after receiving RBP-6000, the procedures at Week 25/Day 169 will serve as the ET assessments.
14. IXRS contacted to confirm study completion or discontinuation status (date and reason for discontinuation).
15. Complete examination (excluding pelvic, breast, and rectal), including general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities, and a brief neurological assessment.
16. Subject's alternative treatment options should be assessed up to two months before EOS. At the EOS visit, if eligible, subjects may enroll in study INDV-6000-301. Alternatively, subjects can start an optional 4 week SUBOXONE program (based on Investigator's discretion).
17. Collect information for the Employment/Support Status, Alcohol, Drug, Legal, Family/Social, and Psychological section only. Follow-up version of the questionnaire (only circled items, no lifetime recall).
18. Complete all ASI-Lite scales. Follow-up version of the questionnaire (only circled items, no lifetime recall).
19. Subjects should be contacted by telephone at 24 hrs ( $\pm 4$  hours) and will be assessed for AEs and any changes to Con Meds. Subjects are not required to return to the site unless the investigator deems it medically necessary.
20. Subjects should be contacted by telephone in order to assess for AEs or Con Meds. Subjects are not required to return to the site unless the investigator deems it medically necessary. Subjects enrolled onto INDV-6000-301 are not required to be contacted.

## Appendix 4 Schedule of Events – RBP-6000 Injection 7 – 9 Visits for *de novo* Subjects

Evaluation	Inj 7	Post Inj 7 24hrs	Inj 8	Post Inj 8 24hrs	Inj 9	Post Inj 9 24hrs
	Wk25 D169	Wk25 D170	Wk29 D197	Wk29 D198	Wk33 D225	Wk33 D226
Window	-2/ +4	+1	-2/ +4	+1	-2/ +4	+1
IWRS	X		X		X	
Vital Signs <sup>1</sup>	X		X		X	
Body Weight	X					
BMI Calculation	X					
Hip-to-Waist Ratio	X					
12-lead ECG <sup>2</sup> (supine ≥ 10 min)	X		X		X	
Hematology/ Serum Chemistry <sup>3</sup>	X		X		X	
Hormone Panel <sup>3</sup>	X					
Urinalysis <sup>3</sup>	X		X		X	
Urine Pregnancy Test <sup>4</sup>	X		X		X	
Urine Drug Screen <sup>5</sup>	X		X		X	
Concomitant Medications	X	X <sup>13</sup>	X	X <sup>13</sup>	X	X <sup>13</sup>
AE Assessment <sup>6</sup>	X	X <sup>13</sup>	X	X <sup>13</sup>	X	X <sup>13</sup>
eC-SSRS (Since last-visit-version) <sup>7</sup>	X		X		X	
TLFB Interview <sup>7</sup>	X		X		X	
Opioid Craving VAS <sup>7</sup>	X		X		X	
COWS <sup>7</sup>	X		X		X	
SOWS <sup>7</sup>	X		X		X	
BDI-II <sup>7</sup>	X		X		X	
BPI <sup>7</sup>	X		X		X	
RBP-6000 Injection	X		X		X	

Evaluation	Inj 7	Post Inj 7 24hrs	Inj 8	Post Inj 8 24hrs	Inj 9	Post Inj 9 24hrs
	Wk25 D169	Wk25 D170	Wk29 D197	Wk29 D198	Wk33 D225	Wk33 D226
Window	-2/ +4	+1	-2/ +4	+1	-2/ +4	+1
Injection Site Grading Scale <sup>8</sup>	X		X		X	
Injection Site Pain VAS <sup>9</sup>	X		X		X	
Injection Site Evaluation <sup>10</sup>	X		X		X	
Behavioral Therapy <sup>11</sup>	X		X		X	
EQ-5D-5L <sup>7</sup>					X	
SF-36v2 <sup>7</sup>					X	
MSQ <sup>7</sup>					X	
Health Insurance <sup>7</sup>	X		X		X	
HCRU <sup>7</sup>	X		X		X	
TEA <sup>7</sup>	X		X		X	
ASI Lite					X <sup>12</sup>	

AE = adverse event; ASI = Addiction Severity Index; BDI-II = Beck Depression Inventory II; BMI = body mass index; BPI = Brief Pain Inventory Short Form; COWS = Clinical Opiate Withdrawal Scale; eC-SSRS = electronic Columbia Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; EQ-5D-5L = EuroQol EQ-5D-5L; HCRU = Healthcare resource utilization; Inj. = injection; IXRS=Interactive voice/web response system; MSQ = Medication Satisfaction Questionnaire; PK = pharmacokinetic/pharmacokinetics; SF-36v2 = 36-Item Short Form Health Survey, Version 2; SC = subcutaneous; SOWS = subjective opiate withdrawal scale; TEA = Treatment Effectiveness Assessment; TLFB = Timeline Followback; VAS = Visual Analog Scale

1. Includes blood pressure, pulse oximetry, pulse rate, respiratory rate, and oral temperature which must be taken after subject is supine  $\geq 3$  minutes. On days injections 2-12 are given, vital signs will be taken  $\leq 60$  minutes prior to SC injection, and 1 hour post SC injection ( $\pm 15$  minutes). For non-injection days, vital signs will be taken at approximately the same time of day as the Day 1 pre-injection vital signs.
2. On days injections 2-12 are given, an ECG will be recorded  $\leq 60$  minutes prior to SC injection, and 1 hour post SC injection ( $\pm 30$  minutes). For non-injection days, an ECG will be performed at approximately the same time of day as the Day 1 pre-injection ECG. All ECGs must be performed prior to labs and PK samples.
3. On injection days, blood and urine samples will be taken  $\leq 60$  minutes prior to SC injection and after the ECGs has been performed.
4. Only for female subjects who are of childbearing potential (not postmenopausal or surgically sterile for at least 1 year).
5. An additional urine drug screen can be done if use is suspected. Oxycodone may not show up in all opiate assays and should be assessed separately.
6. A PK sample will be taken as soon as possible after any SAE is reported. If possible, an additional sample should be collected when the SAE has been resolved.
7. Assessments should be performed prior to RBP-6000 injection and at approximately the same time each day  $\pm 2$  hours.

8. Local injection site grading will be performed at time of SC injection (within 10 minutes) and 1 hour ( $\pm$  15 minutes).
9. Injection Site Pain VAS will be completed by the subject within 1 minute after the completion of the injection and then at 5, 10, 15, 30, and 60 minutes ( $\pm$  5 minutes) post-completion of injection.
10. Injection site will be evaluated for evidence of attempted removal.
11. Additional unscheduled visits for behavioral therapy may be added at the Investigator's discretion.
12. Collect information for the Employment/Support Status, Alcohol, Drug, Legal, Family/Social, and Psychological section only. Follow-up version of the questionnaire (only circled items, no lifetime recall).
13. Subjects should be contacted by telephone at 24 hrs ( $\pm$  4 hours) and will be assessed for AEs and any changes to Con Meds. Subjects are not required to return to the site unless the investigator deems it medically necessary.

## Appendix 5 Schedule of Events – RBP-6000 Injection 10 – 12 Visits and End of Study/Early Termination Visit and Follow-Up for *de novo* Subjects

Evaluation	Inj 10	Post Inj 10 24hrs	Inj 11	Post Inj 11 24hrs	Inj 12	Post Inj 12 24hrs	EOS/ET <sup>12</sup>	Safety Follow-Up <sup>19</sup>
	Wk37 D253	Wk37 D254	Wk41 D281	Wk41 D282	Wk45 D309	Wk45 D310	Wk49 D337	Wk53 D365
Window	-2/ +4	+1	-2/ +4	+1	-2/ +4	+1	-2/ +4	-2/ +4
IWRS	X		X		X		X <sup>13</sup>	
Vital Signs 1	X		X		X		X	
Body Weight	X				X		X	
BMI Calculation	X				X		X	
Hip-to-Waist Ratio	X				X		X	
12-lead ECG (supine ≥ 10 min) <sup>2</sup>	X		X		X		X	
Hematology/ Serum Chemistry <sup>3</sup>	X		X		X		X	
Hormone Panel <sup>3</sup>	X				X		X	
Urinalysis <sup>3</sup>	X		X		X		X	
Urine Pregnancy Test <sup>4</sup>	X		X		X		X	
Serum Pregnancy Test <sup>4</sup>								
Urine Drug Screen <sup>5</sup>	X		X		X		X	
Concomitant Medications	X	X <sup>18</sup>	X	X <sup>18</sup>	X	X <sup>18</sup>	X	X
AE Assessment <sup>6</sup>	X	X <sup>18</sup>	X	X <sup>18</sup>	X	X <sup>18</sup>	X	X
eC-SSRS (Since last-visit-version) <sup>7</sup>	X		X		X		X	
TLFB Interview <sup>7</sup>	X		X		X		X	
Opioid Craving VAS <sup>7</sup>	X		X		X		X	
COWS <sup>7</sup>	X		X		X		X	
SOWS <sup>7</sup>	X		X		X		X	
BDI-II <sup>7</sup>	X		X		X		X	
BPI <sup>7</sup>	X		X		X		X	



Evaluation	Inj 10	Post Inj 10 24hrs	Inj 11	Post Inj 11 24hrs	Inj 12	Post Inj 12 24hrs	EOS/ET <sup>12</sup>	Safety Follow-Up <sup>19</sup>
	Wk37 D253	Wk37 D254	Wk41 D281	Wk41 D282	Wk45 D309	Wk45 D310	Wk49 D337	Wk53 D365
Window	-2/ +4	+1	-2/ +4	+1	-2/ +4	+1	-2/ +4	-2/ +4
RBP-6000 Injection	X		X		X			
Injection Site Grading Scale <sup>8</sup>	X		X		X			
Injection Site Pain VAS <sup>9</sup>	X		X		X			
Injection Site Evaluation <sup>10</sup>	X		X		X		X	
Behavioral Therapy <sup>11</sup>	X		X		X		X	
EQ-5D-5L <sup>7</sup>					X		X	
SF-36v2 <sup>7</sup>					X		X	
MSQ <sup>7</sup>					X		X	
Health Insurance <sup>7</sup>	X		X		X		X	
HCRU <sup>7</sup>	X		X		X		X	
TEA <sup>7</sup>	X		X		X		X	
ASI Lite					X <sup>16</sup>		X <sup>17</sup>	
Physical Examination <sup>14</sup>							X	
Review of Treatment Options <sup>15</sup>			X		X		X	
Alternative Treatment Agreed <sup>15</sup>							X	

AE = adverse event; ASI = Addiction Severity Index; BDI-II = Beck Depression Inventory II; BMI = body mass index; BPI = Brief Pain Inventory Short Form; COWS = Clinical Opiate Withdrawal Scale; eC-SSRS = electronic Columbia Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; EOS/ET = End of Study/Early Termination; EQ-5D-5L = EuroQol EQ-5D-5L; HCRU = Healthcare resource utilization; Inj. = injection; IXRS=Interactive voice/web response system; MSQ = Medication Satisfaction Questionnaire; PK = pharmacokinetic/pharmacokinetics; SF-36v2 = 36-Item Short Form Health Survey, Version 2; SC = subcutaneous; SL = sublingual; SOWS = subjective opiate withdrawal scale; TEA = Treatment Effectiveness Assessment; TLFB = Timeline Followback; VAS = Visual Analog Scale.

- Includes blood pressure, pulse oximetry, pulse rate, respiratory rate, and oral temperature which must be taken after subject is supine  $\geq 3$  minutes. On days injections 2-12 are given, vital signs will be taken  $\leq 60$  minutes prior to SC injection, and 1 hour post SC injection ( $\pm 15$  minutes). For non-injection days, vital signs will be taken at approximately the same time of day as the Day 1 pre-injection vital signs.

2. On days injections 2-12 are given, an ECG will be recorded  $\leq 60$  minutes prior to SC injection, and 1 hour post SC injection ( $\pm 30$  minutes). For non-injection days, an ECG will be performed at approximately the same time of day as the Day 1 pre-injection ECG. All ECGs must be performed prior to labs and PK samples.
3. On injection days, blood and urine samples will be taken  $\leq 60$  minutes prior to SC injection and after the ECGs has been performed.
4. Only for female subjects who are of childbearing potential (not postmenopausal or surgically sterile for at least 1 year).
5. An additional urine drug screen can be done if use is suspected. Oxycodone may not show up in all opiate assays and should be assessed separately.
6. A PK sample will be taken as soon as possible after any SAE is reported. If possible, an additional sample should be collected when the SAE has been resolved.
7. Assessments should be performed prior to RBP-6000 injection and at approximately the same time each day  $\pm 2$  hours.
8. Local injection site grading will be performed at time of SC injection (within 10 minutes) and 1 hour ( $\pm 15$  minutes).
9. Injection Site Pain VAS will be completed by the subject within 1 minute after the completion of the injection and then at 5, 10, 15, 30, and 60 minutes ( $\pm 5$  minutes) post-completion of injection.
10. Injection site will be evaluated for evidence of attempted removal.
11. Additional unscheduled visits for behavioral therapy may be added at the Investigator's discretion.
12. For *de novo* subjects who discontinue participation in this study after receiving RBP-6000, the procedures at Week 49/Day 337 will serve as the ET assessments.
13. IXRS contacted to confirm study completion or discontinuation status (date and reason for discontinuation).
14. Complete examination (excluding pelvic, breast, and rectal), including general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities, and a brief neurological assessment.
15. Subject's alternative treatment options should be assessed up to two months before EOS. At the EOS visit, if eligible, subjects may enroll in study INDV-6000-301. Alternatively, subjects can start an optional 4 week SUBOXONE program (based on Investigator's discretion).
16. Collect information for the Employment/Support Status, Alcohol, Drug, Legal, Family/Social, and Psychological section only. Follow-up version of the questionnaire (only circled items, no lifetime recall).
17. Complete all ASI-Lite scales. Follow-up version of the questionnaire (only circled items, no lifetime recall).
18. Subjects should be contacted by telephone at 24 hrs ( $\pm 4$  hours) and will be assessed for AEs and any changes to Con Meds. Subjects are not required to return to the site unless the investigator deems it medically necessary.
19. Subjects should be contacted by telephone in order to assess for AEs or Con Meds. Subjects are not required to return to the site unless the investigator deems it medically necessary. Subjects enrolled onto INDV-6000-301 are not required to be contacted.

## Appendix 6 Pharmacokinetic Sampling Schedule

Sample Number <sup>1</sup>	Sample Class	Time	Study Phase	Comments
1	PK	Day 1	Treatment phase (SC)	Within 1 hour prior to 1 <sup>st</sup> SC injection
2	PK	Day 15	Treatment phase (SC)	Post 1 <sup>st</sup> SC injection
3	PK	Day 29	Treatment phase (SC)	Within 1 hour prior to 2 <sup>nd</sup> SC injection
4	PK	Day 43	Treatment phase (SC)	Post 2 <sup>nd</sup> SC injection
5	PK	Day 57	Treatment phase (SC)	Within 1 hour prior to 3 <sup>rd</sup> SC injection
6	PK	Day 71	Treatment phase (SC)	Post 3 <sup>rd</sup> SC injection
7	PK	Day 85	Treatment phase (SC)	Within 1 hour prior to 4 <sup>th</sup> SC injection
8	PK	Day 99	Treatment phase (SC)	Post 4 <sup>th</sup> SC injection
9	PK	Day 113	Treatment phase (SC)	Within 1 hour prior to 5 <sup>th</sup> SC injection
10	PK	Day 127	Treatment phase (SC)	Post 5 <sup>th</sup> SC injection
11	PK	Day 141	Treatment phase (SC)	Within 1 hour prior to 6 <sup>th</sup> SC injection
12	PK	Day 169 or ET Visit	Treatment phase (SC)	Post 6 <sup>th</sup> SC injection

PK = pharmacokinetic/pharmacokinetics; SC = subcutaneous

<sup>1</sup> Blood samples for PK analysis will be collected from roll-over subjects only (not *de novo*). Once at least 75 roll-over subjects have completed Injection 6 (Week 25, Day 169) no more PK samples will be required to be collected from the roll-over subjects for the duration of the study.

However, for all subjects (de novo and roll-over), a PK sample will be taken as soon as possible after any SAE is reported. If possible, an additional sample should be collected when the SAE has been resolved.

## Appendix 7 SUBOXONE® (Buprenorphine/Naloxone) Sublingual Film Full Prescribing Information

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SUBOXONE safely and effectively. See full prescribing information for SUBOXONE.

SUBOXONE® (buprenorphine and naloxone) sublingual film, for sublingual or buccal use CIII

Initial U.S. Approval: 2002

#### RECENT MAJOR CHANGES

Dosage and Administration, Method of Administration (2.3)	09/2015
Warnings and Precautions, Neonatal Opioid Withdrawal Syndrome (5.5)	06/2016

#### INDICATIONS AND USAGE

SUBOXONE sublingual film is a partial-opioid agonist indicated for treatment of opioid dependence. Prescription use of this product is limited under the Drug Addiction Treatment Act. (1)

#### DOSAGE AND ADMINISTRATION

- For patients dependent on short-acting opioid products who are in opioid withdrawal; on Day 1, administer up to 8 mg/2 mg SUBOXONE sublingual film (in divided doses). On Day 2, administer up to 16 mg/4 mg of SUBOXONE sublingual film as a single dose. (2.1)
- For patients dependent on methadone or long-acting opioid products, induction onto sublingual buprenorphine monotherapy is recommended on Days 1 and 2 of treatment. (2.1)
- For maintenance treatment, the target dosage of SUBOXONE sublingual film is usually 16 mg/4 mg as a single daily dose. (2.2)
- Sublingual Administration: Place one film under the tongue, close to the base on the left or right side, and allow to completely dissolve. Buccal Administration: Place one film on the inside of the left or right cheek and allow to completely dissolve.
- SUBOXONE sublingual film must be administered whole. Do not cut, chew, or swallow SUBOXONE sublingual film (2.3)

#### DOSAGE FORMS AND STRENGTHS

Sublingual film: 2 mg buprenorphine with 0.5 mg naloxone, 4 mg buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone and 12 mg buprenorphine with 3 mg naloxone. (3)

#### CONTRAINDICATIONS

Hypersensitivity to buprenorphine or naloxone. (4)

#### WARNINGS AND PRECAUTIONS

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. (5.1)
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol). (5.2)
- Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription. (5.3)

- Store SUBOXONE sublingual film safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children. (5.4)
- Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy (5.5)
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome. (5.6)
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events. (5.7)
- Do not administer SUBOXONE sublingual film to patients with known hypersensitivity to buprenorphine or naloxone. (5.8)
- An opioid withdrawal syndrome is likely to occur with parenteral misuse of SUBOXONE sublingual film by individuals physically dependent on full opioid agonists, or by sublingual or buccal administration before the agonist effects of other opioids have subsided. (5.9)
- SUBOXONE sublingual film is not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose. (5.10)
- Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment (5.11)
- Caution patients about the risk of driving or operating hazardous machinery. (5.12)

#### ADVERSE REACTIONS

Adverse events commonly observed with the sublingual/buccal administration of the SUBOXONE sublingual film were oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Indivior Inc. at 1-877-782-6966 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing. (7.1)
- Use caution in prescribing SUBOXONE sublingual film for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse. (7.3)

#### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing mothers: Caution should be exercised when administered to a nursing woman. (8.3)
- Safety and effectiveness of SUBOXONE sublingual film in patients below the age of 16 has not been established. (8.4)
- Administer SUBOXONE sublingual film with caution to elderly or debilitated patients. (8.5)
- Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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\* Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

SUBOXONE sublingual film is indicated for treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

**Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.**

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Induction

Prior to induction, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid products), the time since last opioid use, and the degree or level of opioid dependence. To avoid precipitating an opioid withdrawal syndrome, the first dose of buprenorphine/naloxone should be started only when objective signs of moderate withdrawal appear.

On Day 1, an induction dosage of up to 8 mg/2 mg SUBOXONE sublingual film is recommended. Clinicians should start with an initial dose of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone and may titrate upwards in 2 or 4 mg increments of buprenorphine, at approximately 2-hour intervals, under supervision, to 8 mg/2 mg buprenorphine/naloxone based on the control of acute withdrawal symptoms.

On Day 2, a single daily dose of up to 16 mg/4 mg SUBOXONE sublingual film is recommended.

Because the exposure to naloxone is somewhat higher after buccal than after sublingual administration, it is recommended that the sublingual site of administration be used during induction to minimize exposure to naloxone, to reduce the risk of precipitated withdrawal.

Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits.

#### ***Patients dependent on methadone or long-acting opioid products***

Patients dependent upon methadone or long-acting opioid products may be more susceptible to precipitated and prolonged withdrawal during induction than those on short-acting opioid products. Buprenorphine/naloxone combination products have not been evaluated in adequate and well-controlled studies for induction in patients on long-acting opioid products, and contain naloxone, which is absorbed in small amounts by the sublingual route and could cause worse precipitated and prolonged withdrawal. For this reason, **buprenorphine monotherapy is recommended in patients taking long-acting opioids when used according to approved administration instructions.** Following induction, the patient may then be transitioned to once-daily SUBOXONE sublingual film.

#### ***Patients dependent on heroin or other short-acting opioid products***

Patients dependent on heroin or short-acting opioid products may be inducted with either SUBOXONE sublingual film or with sublingual buprenorphine monotherapy. The first dose of SUBOXONE sublingual

film or buprenorphine should be administered when objective signs of moderate opioid withdrawal appear, and not less than 6 hours after the patient last used an opioid.

It is recommended that an adequate maintenance dose, titrated to clinical effectiveness, be achieved as rapidly as possible. In some studies, a too-gradual induction over several days led to a high rate of drop-out of buprenorphine patients during the induction period.

## **2.2 Maintenance**

For maintenance, SUBOXONE sublingual film may be administered buccally or sublingually. The dosage of SUBOXONE sublingual film from Day 3 onwards should be progressively adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.

After treatment induction and stabilization, the maintenance dose of SUBOXONE sublingual film is generally in the range of 4 mg/1 mg buprenorphine/naloxone to 24 mg/6 mg buprenorphine/naloxone per day depending on the individual patient and clinical response. The recommended target dosage of SUBOXONE sublingual film during maintenance is 16 mg/4 mg buprenorphine/naloxone/day as a single daily dose. Dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage.

## **2.3 Method of Administration**

SUBOXONE sublingual film must be administered whole. Do not cut, chew, or swallow SUBOXONE sublingual film.

### *Sublingual Administration*

Place one film under the tongue, close to the base on the left or right side. If an additional film is necessary to achieve the prescribed dose, place an additional film sublingually on the opposite side from the first film. Place the film in a manner to minimize overlapping as much as possible. The film must be kept under the tongue until the film is completely dissolved. If a third film is necessary to achieve the prescribed dose, place it under the tongue on either side after the first 2 films have dissolved.

### *Buccal Administration*

Place one film on the inside of the right or left cheek. If an additional film is necessary to achieve the prescribed dose, place an additional film on the inside of the opposite cheek. The film must be kept on the inside of the cheek until the film is completely dissolved. If a third film is necessary to achieve the prescribed dose, place it on the inside of the right or left cheek after the first two films have dissolved.

**SUBOXONE sublingual film should NOT be moved after placement. Proper administration technique should be demonstrated to the patient.**

## **2.4 Clinical Supervision**

Treatment should be initiated with supervised administration, progressing to unsupervised administration as the patient's clinical stability permits. SUBOXONE sublingual film is subject to diversion and abuse. When determining the prescription quantity for unsupervised administration, consider the patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of take-home medication.

Ideally patients should be seen at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of the treatment plan, and overall patient progress.

Once a stable dosage has been achieved and patient assessment (e.g., urine drug screening) does not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of medication who are making progress toward their treatment objectives. Continuation or modification of pharmacotherapy should be based on the physician's evaluation of treatment outcomes and objectives such as:

1. Absence of medication toxicity.
2. Absence of medical or behavioral adverse effects.
3. Responsible handling of medications by the patient.
4. Patient's compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities).
5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use).

If treatment goals are not being achieved, the physician should re-evaluate the appropriateness of continuing the current treatment.

## **2.5 Patients With Hepatic Impairment**

Severe hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine, and moderate hepatic impairment also results in a reduced clearance of naloxone to a greater extent than buprenorphine. Because the doses of this fixed combination product cannot be individually titrated, the combination product should generally be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment [see *Warnings and Precautions (5.11)*].

## **2.6 Unstable Patients**

Physicians will need to decide when they cannot appropriately provide further management for particular patients. For example, some patients may be abusing or dependent on various drugs, or unresponsive to psychosocial intervention such that the physician does not feel that he/she has the expertise to manage the patient. In such cases, the physician may want to assess whether to refer the patient to a specialist or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.



## 2.7 Stopping Treatment

The decision to discontinue therapy with SUBOXONE sublingual film after a period of maintenance should be made as part of a comprehensive treatment plan. Taper patients to avoid opioid withdrawal signs and symptoms.

## 2.8 Switching Between Buprenorphine or Buprenorphine and Naloxone Sublingual Tablets and SUBOXONE Sublingual Film

Patients being switched between buprenorphine and naloxone or buprenorphine only sublingual tablets and SUBOXONE sublingual film should be started on the corresponding dosage of the previously administered product. However, dosage adjustments may be necessary when switching between buprenorphine products. Not all strengths and combinations of the SUBOXONE sublingual films are bioequivalent to the SUBOXONE (buprenorphine and naloxone) sublingual tablets as observed in pharmacokinetic studies [see *Clinical Pharmacology* (12.3)]. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to film or vice-versa. Patients should be monitored for symptoms related to over-dosing or under-dosing.

## 2.9 Switching Between SUBOXONE Sublingual Film Strengths

As indicated in Table 1, the sizes and the compositions of the four units of SUBOXONE sublingual films, i.e.,

2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg and the 12 mg/3 mg units, are different from one another. If patients switch between various combinations of lower and higher strength units of SUBOXONE sublingual films to obtain the same total dose, (e.g., from three 4 mg/1 mg units to a single 12 mg/3 mg unit, or vice-versa), systemic exposures of buprenorphine and naloxone may be different and patients should be monitored for over-dosing or under-dosing. For this reason, pharmacist should not substitute one or more film strengths for another without approval of the prescriber.

**Table 1. Comparison of Available SUBOXONE Sublingual Film Strengths by Dimensions and Drug Concentrations.**

SUBOXONE sublingual film unit strength (buprenorphine/naloxone)	SUBOXONE sublingual film unit dimensions	Buprenorphine Concentration % (w/w)	Naloxone Concentration % (w/w)
2 mg/0.5 mg	22.0 mm x 12.8 mm	5.4	1.53
4 mg/1 mg (2 times the length of the 2 mg/0.5 mg unit)	22.0 mm x 25.6 mm	5.4	1.53
8 mg/2 mg	22.0 mm x 12.8 mm	17.2	4.88
12 mg/3 mg (1.5 times the length of the 8 mg/2 mg unit)	22.0 mm X 19.2 mm	17.2	4.88

## 2.10 Switching Between Sublingual and Buccal Sites of Administration

The systemic exposure of buprenorphine between buccal and sublingual administration of SUBOXONE sublingual film is similar. Therefore, once induction is complete, patients can switch between buccal and sublingual administration without significant risk of under or overdosing.

## 3 DOSAGE FORMS AND STRENGTHS

SUBOXONE sublingual film is supplied as an orange rectangular film with a white printed logo in four dosage strengths:

- buprenorphine/naloxone 2 mg/0.5 mg,
- buprenorphine/naloxone 4 mg/1 mg,
- buprenorphine/naloxone 8 mg/2 mg and
- buprenorphine/naloxone 12 mg/3 mg

## 4 CONTRAINDICATIONS

SUBOXONE sublingual film should not be administered to patients who have been shown to be hypersensitive to buprenorphine or naloxone as serious adverse reactions, including anaphylactic shock, have been reported [*see Warnings and Precautions (5.7)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Abuse Potential

Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. Prescribe and dispense buprenorphine with appropriate precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the home. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits [*see Drug Abuse and Dependence (9.2)*].

### 5.2 Respiratory Depression

Buprenorphine, particularly when taken by the IV route, in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death. Many, but not all, post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines involved misuse by self-injection. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other CNS depressant drugs. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with SUBOXONE sublingual film [*see Drug Interactions (7.3)*].

**In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.**

SUBOXONE sublingual film should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

### 5.3 CNS Depression

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. Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription [see *Drug Interactions* (7.3)].

### 5.4 Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Store buprenorphine-containing medications safely out of the sight and reach of children.

### 5.5 Neonatal Opioid Withdrawal Syndrome

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorized or illicit. Unlike opioid withdrawal syndrome in adults, NOWS may be life-threatening if not recognized and treated in the neonate. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly [see *Specific Populations* (8.1)]. Advise pregnant women receiving opioid addiction treatment with SUBOXONE of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Specific Populations* (8.1)]. This risk must be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Therefore, prescribers should discuss the importance and benefits of management of opioid addiction throughout pregnancy.

### 5.6 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Buprenorphine can be abused in a manner similar to other opioids. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion [see *Drug Abuse and Dependence* (9.3)].

### 5.7 Hepatitis, Hepatic Events

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

prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

### **5.8 Allergic Reactions**

Cases of hypersensitivity to buprenorphine and naloxone containing products have been reported both in clinical trials and in the post-marketing experience. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, hives, and pruritus. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to the use of SUBOXONE sublingual film.

### **5.9 Precipitation of Opioid Withdrawal Signs and Symptoms**

Because it contains naloxone, SUBOXONE sublingual film is likely to produce withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone. Because of the partial agonist properties of buprenorphine, SUBOXONE sublingual film may precipitate opioid withdrawal signs and symptoms in such persons if administered before the agonist effects of the opioid have subsided.

### **5.10 Use in Opioid Naïve Patients**

There have been reported deaths of opioid naïve individuals who received a 2 mg dose of buprenorphine as a sublingual tablet for analgesia. SUBOXONE sublingual film is not appropriate as an analgesic.

### **5.11 Use in Patients With Impaired Hepatic Function**

Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. Because hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine, the doses of buprenorphine and naloxone in this fixed-dose combination product cannot be individually titrated. Therefore, patients with severe hepatic impairment will be exposed to substantially higher levels of naloxone than patients with normal hepatic function. This may result in an increased risk of precipitated withdrawal at the beginning of treatment (induction) and may interfere with buprenorphine's efficacy throughout treatment. In patients with moderate hepatic impairment, the differential reduction of naloxone clearance compared to buprenorphine clearance is not as great as in subjects with severe hepatic impairment. Therefore, buprenorphine/naloxone products are not recommended for initiation of treatment (induction) in patients with moderate hepatic impairment due to the increased risk of precipitated withdrawal. However, buprenorphine/naloxone products may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone. However, patients should be carefully monitored and consideration given to the possibility of naloxone interfering with buprenorphine's efficacy [*see Use in Specific Populations (8.6)*].

### **5.12 Impairment of Ability to Drive or Operate Machinery**

SUBOXONE sublingual film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during treatment induction and dose adjustment. Patients should be cautioned about driving or operating hazardous machinery until they are reasonably certain that SUBOXONE sublingual film therapy does not adversely affect his or her ability to engage in such activities.

### **5.13 Orthostatic Hypotension**

Like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory patients.

### **5.14 Elevation of Cerebrospinal Fluid Pressure**

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

### **5.15 Elevation of Intracholedochal Pressure**

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

### **5.16 Effects in Acute Abdominal Conditions**

As with other opioids, buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

### **5.17 General Precautions**

SUBOXONE sublingual film should be administered with caution in debilitated patients and those with myxedema or hypothyroidism, adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

## **6 ADVERSE REACTIONS**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

### **6.1 Clinical Trials Experience**

The safety of SUBOXONE sublingual film is supported by clinical trials using SUBUTEX (buprenorphine) sublingual tablets and SUBOXONE (buprenorphine and naloxone) sublingual tablets, and other trials using buprenorphine sublingual solutions, as well as an open-label study in 194 patients treated with SUBOXONE sublingual film administered sublingually and 188 patients treated with the film administered buccally. In total, safety data from clinical studies are available from over 3000 opioid-dependent subjects exposed to buprenorphine at doses in the range used in the treatment of opioid dependence. Few differences in the adverse event profile were noted with regard to sublingually and buccally administered SUBOXONE sublingual film, SUBOXONE (buprenorphine and naloxone) sublingual tablets, SUBUTEX (buprenorphine) sublingual tablets and a buprenorphine ethanolic sublingual solution.

The most common adverse event (>1%) associated with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia. Other adverse events were constipation, glossodynia, oral mucosal erythema, vomiting, intoxication, disturbance in attention, palpitations, insomnia, withdrawal syndrome, hyperhidrosis, and blurred vision.

The most common adverse events associated with the buccal administration were similar to those observed with sublingual administration of the film.

Other adverse event data were derived from larger, controlled studies of SUBOXONE (buprenorphine and naloxone) sublingual tablets and SUBUTEX (buprenorphine) tablets and of buprenorphine sublingual solution. In a comparative study of SUBOXONE (buprenorphine and naloxone) sublingual tablets and SUBUTEX (buprenorphine) sublingual tablets, adverse event profiles were similar for subjects treated with 16 mg/4 mg SUBOXONE (buprenorphine and naloxone) sublingual tablets or 16 mg SUBUTEX (buprenorphine) sublingual tablets. The following adverse events were reported to occur by at least 5% of patients in a 4 week study of SUBOXONE (buprenorphine and naloxone) sublingual tablets and SUBUTEX (buprenorphine) sublingual tablets.

**Table 2. Adverse Events (≥ 5%) by Body System and Treatment Group in a 4 Week Study**

<b>Body System/ Adverse Event (COSTART Terminology)</b>	<b>SUBOXONE (buprenorphine and naloxone) sublingual tablets 16 mg/4 mg/day N=107 n (%)</b>	<b>SUBUTEX (buprenorphine) sublingual tablets 16 mg/day N=103 n (%)</b>	<b>Placebo N=107 n (%)</b>
<b>Body as a Whole</b>			
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
<b>Cardiovascular System</b>			
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
<b>Digestive System</b>			
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
<b>Nervous System</b>			
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
<b>Respiratory System</b>			
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)

<b>Skin And Appendages</b>			
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of a buprenorphine ethanolic solution, over a range of doses in four months of treatment. Table 3 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled trial.

**Table 3. Adverse Events (≥5%) by Body System and Treatment Group in a 16 Week Study**

<b>Body System/ Adverse Event (COSTART Terminology)</b>	<b>Buprenorphine Dose</b>				
	<b>Very Low* N=184 n (%)</b>	<b>Low* N=180 n (%)</b>	<b>Moderate* N=186 n (%)</b>	<b>High* N=181 n (%)</b>	<b>Total* N=731 n (%)</b>
<b>Body as a Whole</b>					
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%)
<b>Digestive System</b>					
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%)
<b>Nervous System</b>					
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%)
<b>Respiratory System</b>					
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%)
<b>Skin and Appendages</b>					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
<b>Special Senses</b>					
Runny eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

\*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

The safety of SUBOXONE sublingual film during treatment induction is supported by a clinical trial using 16 patients treated with SUBOXONE sublingual film and 18 treated with a buprenorphine-only sublingual film. Few differences in the adverse event profiles were noted between SUBOXONE sublingual film and the buprenorphine-only sublingual film.

The most common adverse event occurring during treatment induction and the 3 days following induction using SUBOXONE sublingual film was restlessness. Other adverse events were anxiety, piloerection, stomach discomfort, irritability, headache, rhinorrhea, cold sweat, arthralgia, and lacrimation increased.

Four subjects left the study early on the first day of sublingual film administration. However, there was not evidence to suggest that any of the four subjects experienced precipitated withdrawal secondary to the administration of buprenorphine or buprenorphine/naloxone sublingual films.



## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SUBOXONE sublingual film. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The most frequently reported postmarketing adverse events were peripheral edema, stomatitis, glossitis, and blistering and ulceration of the mouth or tongue.

## 7 DRUG INTERACTIONS

### 7.1 Cytochrome P-450 3A4 (CYP3A4) Inhibitors and Inducers

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when SUBOXONE sublingual film is given concurrently with agents that affect CYP3A4 activity. The concomitant use of SUBOXONE sublingual film with CYP3A4 inhibitors (e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored and may require dose-reduction of one or both agents.

The interaction of buprenorphine with CYP3A4 inducers has not been studied; therefore, it is recommended that patients receiving SUBOXONE sublingual film be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., efavirenz, phenobarbital, carbamazepine, phenytoin, rifampicin) are coadministered [*see Clinical Pharmacology (12.3)*].

### 7.2 Antiretrovirals

Three classes of antiretroviral agents have been evaluated for CYP3A4 interactions with buprenorphine. Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine and etravirine are known CYP3A inducers whereas delavirdine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects. It is recommended that patients who are on chronic buprenorphine treatment have their dose monitored if NNRTIs are added to their treatment regimen. Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. Monitoring of patients taking buprenorphine and atazanavir with and without ritonavir is recommended, and dose reduction of buprenorphine may be warranted.

### 7.3 Benzodiazepines

There have been a number of postmarketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines. In many, but not all, of these cases, buprenorphine was misused by self-injection. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full

opioid agonists. SUBOXONE sublingual film should be prescribed with caution to patients taking benzodiazepines or other drugs that act on the CNS, regardless of whether these drugs are taken on the advice of a physician or are being abused/misused. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBOXONE sublingual film, and should also be cautioned to use benzodiazepines concurrently with SUBOXONE sublingual film only as directed by their physician.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### *Risk Summary*

There are no adequate and well-controlled studies of SUBOXONE sublingual film or buprenorphine/naloxone in pregnant women. Limited published data on use of buprenorphine, the active ingredient in SUBOXONE sublingual film, in pregnancy, have not shown an increased risk of major malformations. All pregnancies, regardless of drug exposure, have a background risk of 2% to 4% for major birth defects, and 15% to 20% for pregnancy loss. Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant doses. Pre- and postnatal development studies in rats demonstrated dystocia, increased neonatal deaths, and developmental delays. No clear teratogenic effects were seen with a range of doses equivalent to or greater than the human dose. However, in a few studies, some events such as acephalus, omphalocele, and skeletal abnormalities were observed but these findings were not clearly treatment-related. Embryofetal death was also observed in both rats and rabbits.

SUBOXONE sublingual film should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### *Clinical Considerations*

##### *Disease-associated maternal and embryo-fetal risk*

Untreated opioid addiction in pregnancy is associated with adverse obstetrical outcomes such as low birth weight, preterm birth, and fetal death. In addition, untreated opioid addiction often results in continued or relapsing illicit opioid use.

##### *Fetal/neonatal adverse reactions*

Neonatal opioid withdrawal syndrome may occur in newborn infants of mothers who are receiving treatment with SUBOXONE.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and/or failure to gain weight. Signs of neonatal withdrawal usually occur in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly [see *Warnings and Precautions (5.5)*].

##### *Labor or Delivery*

As with all opioids, use of buprenorphine prior to delivery may result in respiratory depression in the newborn. Closely monitor neonates for signs of respiratory depression. An opioid antagonist such as naloxone should be available for reversal of opioid induced respiratory depression in the neonate.

## *Data*

### *Human Data*

Studies have been conducted to evaluate neonatal outcomes in women exposed to buprenorphine during pregnancy. Limited published data on malformations from trials, observational studies, case series, and case reports on buprenorphine use in pregnancy have not shown an increased risk of major malformations. Based on these studies the incidence of neonatal abstinence syndrome is not clear and there does not appear to be a dose-response relationship.

### *Animal Data*

Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the recommended human daily dose of 16 mg on a mg/m<sup>2</sup> basis). Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis).

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis). Fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis). An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices. Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis).

### **8.3 Nursing Mothers**

#### *Risk Summary*

Based on two studies in 13 lactating women, buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine, and available data have not shown adverse reactions in breastfed infants. There are no data on the combination product buprenorphine/naloxone in breastfeeding, however oral absorption of naloxone is minimal. Caution should be exercised when SUBOXONE sublingual film is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBOXONE sublingual film and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

#### *Clinical Considerations*

Advise the nursing mother taking SUBOXONE sublingual film to monitor the infant for increased drowsiness and breathing difficulties.

#### *Data*

Based on limited data from a study of 6 lactating women who were taking a median oral dose of buprenorphine of 0.29 mg/kg/day 5 to 8 days after delivery, breast milk contained a median infant dose of 0.42 mcg/kg/day of buprenorphine and 0.33 mcg/kg/day of norbuprenorphine, which are equal to 0.2% and 0.12% of the maternal weight-adjusted dose.

Based on limited data from a study of 7 lactating women who were taking a median oral dose of buprenorphine of 7 mg/day an average of 1.12 months after delivery, the mean milk concentrations of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L respectively. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, which are 0.38% and 0.18% of the maternal weight-adjusted dose.

No adverse reactions were observed in the infants in these two studies.

### **8.4 Pediatric Use**

The safety and effectiveness of SUBOXONE sublingual film have not been established in pediatric patients. This product is not appropriate for the treatment of neonatal abstinence syndrome in neonates, because it contains naloxone, an opioid antagonist.

## 8.5 Geriatric Use

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

## 8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone has been evaluated in a pharmacokinetic study. Both drugs are extensively metabolized in the liver. While no clinically significant changes have been observed in subjects with mild hepatic impairment; the plasma levels have been shown to be higher and half-life values have been shown to be longer for both buprenorphine and naloxone in subjects with moderate and severe hepatic impairment. The magnitude of the effects on naloxone are greater than that on buprenorphine in both moderately and severely impaired subjects. The difference in magnitude of the effects on naloxone and buprenorphine are greater in subjects with severe hepatic impairment than in subjects with moderate hepatic impairment, and therefore the clinical impact of these effects is likely to be greater in patients with severe hepatic impairment than in patients with moderate hepatic impairment. Buprenorphine/naloxone products should be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment [see *Warnings and Precautions (5.11) and Clinical Pharmacology (12.3)*].

## 8.7 Renal Impairment

No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine. The effects of renal failure on naloxone pharmacokinetics are unknown.

# 9 DRUG ABUSE AND DEPENDENCE

## 9.1 Controlled Substance

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

**Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.**

## 9.2 Abuse

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for more intensive and structured treatment.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

The physician may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal requests of medication prescribed.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper handling and storage of the medication are appropriate measures that help to limit abuse of opioid drugs.

### 9.3 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset [see *Warnings and Precautions (5.5)*].

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy [see *Warnings and Precautions (5.5)*].

## 10 OVERDOSAGE

The manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.

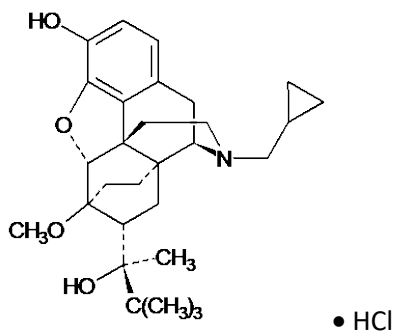
In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully. When respiratory or cardiac functions are depressed, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, IV fluids, vasopressors, and other supportive measures should be employed as indicated.

**In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.**

## 11 DESCRIPTION

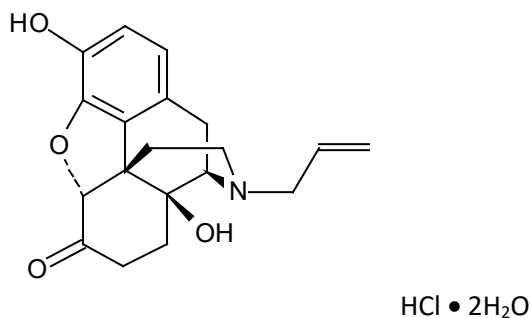
SUBOXONE (buprenorphine and naloxone) sublingual film is an orange film, imprinted with a logo identifying the product and strength in white ink. It contains buprenorphine HCl, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist, and naloxone HCl dihydrate, an opioid receptor antagonist, at a ratio of 4:1 (ratio of free bases). It is intended for sublingual or buccal administration and is available in four dosage strengths, 2 mg buprenorphine with 0.5 mg naloxone, 4 mg buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone and 12 mg buprenorphine with 3 mg naloxone. Each film also contains polyethylene oxide, hydroxypropyl methylcellulose, maltitol, acesulfame potassium, lime flavor, citric acid, sodium citrate, FD&C yellow #6, and white ink.

Chemically, buprenorphine HCl is (2S)-2-[17-Cyclopropylmethyl-4,5 $\alpha$ -epoxy-3-hydroxy-6-methoxy-6 $\alpha$ ,14-ethano-14 $\alpha$ -morphinan-7 $\alpha$ -yl]-3,3-dimethylbutan-2-ol hydrochloride. It has the following chemical structure:



Buprenorphine HCl has the molecular formula  $C_{29}H_{41}NO_4 \cdot HCl$  and the molecular weight is 504.10. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane.

Chemically, naloxone HCl dihydrate is 17-Allyl-4,5  $\alpha$ -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. It has the following chemical structure:



Naloxone hydrochloride dihydrate has the molecular formula  $C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$  and the molecular weight is 399.87. It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol, and practically insoluble in toluene and ether.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

SUBOXONE sublingual film contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally.

### 12.2 Pharmacodynamics

#### 11.1.1.1 Subjective Effects

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

In opioid-experienced subjects who were not physically dependent, acute sublingual doses of buprenorphine/naloxone tablets produced opioid agonist effects which reached a maximum between doses of 8 mg/2 mg and 16 mg/4 mg buprenorphine/naloxone.

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

#### 11.1.1.2 *Physiologic Effects*

Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory, and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O<sub>2</sub> saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3 hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O<sub>2</sub> saturation to the same degree.

#### ***Effect of Naloxone***

Physiologic and subjective effects following acute sublingual administration of buprenorphine tablets and buprenorphine/naloxone tablets were similar at equivalent dose levels of buprenorphine. Naloxone had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. Buprenorphine/naloxone, when administered sublingually to an opioid-dependent cohort, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. This finding suggests that the naloxone in buprenorphine/naloxone tablets may deter injection of buprenorphine/naloxone tablets by persons with active substantial heroin or other full mu-opioid dependence. However, clinicians should be aware that some opioid-dependent persons, particularly those with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine, abuse buprenorphine/naloxone combinations by the intravenous or intranasal route. In methadone-maintained patients and heroin-dependent subjects, IV administration of buprenorphine/naloxone combinations precipitated opioid withdrawal signs and symptoms and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal signs and symptoms that were ratio-dependent; the most intense withdrawal signs and symptoms were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio.



### 12.3 Pharmacokinetics

#### ***Absorption***

In several pharmacokinetic studies following the administration of different dosages, a dose of one or two of the 2 mg/0.5 mg SUBOXONE sublingual films administered sublingually or buccally showed comparable relative bioavailability to the same total dose of SUBOXONE sublingual tablets. In contrast, one 8 mg/2 mg and one 12 mg/3 mg SUBOXONE sublingual films administered sublingually or buccally showed higher relative bioavailability for both buprenorphine and naloxone compared to the same total dose of SUBOXONE sublingual tablets. A combination of one 8 mg/2 mg and two 2 mg/0.5 mg SUBOXONE sublingual films (total dose of 12 mg/ 3 mg) administered sublingually showed comparable relative bioavailability to the same total dose of SUBOXONE sublingual tablets, while buccally administered SUBOXONE sublingual films showed higher relative bioavailability. Table 4, below, illustrates the relative increase in exposure to buprenorphine and naloxone associated with SUBOXONE sublingual films compared to SUBOXONE tablets, and shows the effect of route of administration [see *Dosage and Administration (2.8 and 2.9)*].

Across relevant pharmacokinetic studies, the pharmacokinetic parameters and exposures derived from the buccal and sublingual administrations of SUBOXONE sublingual film were comparable to one another.

Table 4. Changes in Pharmacokinetic Parameters for SUBOXONE Sublingual Film Administered Sublingually or Buccally in Comparison to SUBOXONE Sublingual Tablet

Dosage	PK Parameter	Increase in Buprenorphine			PK Parameter	Increase in Naloxone		
		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual
1 x 2 mg/0.5 mg	C <sub>max</sub>	22%	25%	-	C <sub>max</sub>	-	-	-
	AUC <sub>0-last</sub>	-	19%	-	AUC <sub>0-last</sub>	-	-	-
2 x 2 mg/0.5 mg	C <sub>max</sub>	-	21%	21%	C <sub>max</sub>	-	17%	21%
	AUC <sub>0-last</sub>	-	23%	16%	AUC <sub>0-last</sub>	-	22%	24%
1 x 8 mg/2 mg	C <sub>max</sub>	28%	34%	-	C <sub>max</sub>	41%	54%	-
	AUC <sub>0-last</sub>	20%	25%	-	AUC <sub>0-last</sub>	30%	43%	-
1 x 12 mg/3 mg	C <sub>max</sub>	37%	47%	-	C <sub>max</sub>	57%	72%	9%
	AUC <sub>0-last</sub>	21%	29%	-	AUC <sub>0-last</sub>	45%	57%	-
1 x 8 mg/2 mg plus 2 x 2 mg/0.5 mg	C <sub>max</sub>	-	27%	13%	C <sub>max</sub>	17%	38%	19%
	AUC <sub>0-last</sub>	-	23%	-	AUC <sub>0-last</sub>	-	30%	19%
1 x 16 mg/4 mg film	C <sub>max</sub>	34%	29%	7%	C <sub>max</sub>	44%	46%	9%
	AUC <sub>0-last</sub>	32%	-	-	AUC <sub>0-last</sub>	49%	36%	3%

Note: 1. the 16 mg/4 mg strength film is not marketed; it is compositionally proportional to the 8 mg/2 mg strength film and has the same size of 2 x 8 mg/2 mg film. 2. – represents no change when the 90% confidence intervals for the geometric mean ratios of the C<sub>max</sub> and AUC<sub>0-last</sub> values are within the 80% to 125% limit. 3. There are no data for the 4 mg/1 mg strength film; it is compositionally proportional to 2 mg/0.5 mg strength film and has the same size of 2 x 2 mg/0.5 mg film strength.

### ***Distribution***

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

Naloxone is approximately 45% protein bound, primarily to albumin.

### ***Elimination***

Buprenorphine is metabolized and eliminated in urine and feces. Naloxone undergoes metabolism as well. When SUBOXONE sublingual film is administered sublingually or buccally, buprenorphine has a mean elimination half-life ranging from 24 to 42 hours and naloxone has a mean elimination half-life ranging from 2 to 12 hours.

### ***Metabolism***

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors *in*

*vitro*; however, it has not been studied clinically for opioid-like activity. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

#### **Excretion**

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated). Based on all studies performed with sublingually and buccally administered SUBOXONE sublingual film, buprenorphine has a mean elimination half-life from plasma ranging from 24 to 42 hours and naloxone has a mean elimination half-life from plasma ranging from 2 to 12 hours.

#### **DRUG-DRUG INTERACTIONS**

**CYP3A4 Inhibitors and Inducers:** Subjects receiving SUBOXONE sublingual film should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving SUBOXONE sublingual film be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are coadministered [see *Drug Interactions* (7.1)].

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

#### **SPECIAL POPULATIONS:**

**Hepatic Impairment:** In a pharmacokinetic study, the disposition of buprenorphine and naloxone were determined after administering a SUBOXONE 2.0/0.5 mg (Buprenorphine/Naloxone) sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine and naloxone in patients with hepatic impairment were compared to disposition in subjects with normal hepatic function.

In subjects with mild hepatic impairment, the changes in mean  $C_{max}$ ,  $AUC_{0-last}$ , and half-life values of both buprenorphine and naloxone were not clinically significant. No dosing adjustment is needed in patients with mild hepatic impairment.

For subjects with moderate and severe hepatic impairment, mean  $C_{max}$ ,  $AUC_{0-last}$ , and half-life values of both buprenorphine and naloxone were increased; the effects on naloxone are greater than that on buprenorphine (Table 5).

Table 5. Changes in Pharmacokinetic Parameters in Subjects With Moderate and Severe Hepatic Impairment

Hepatic	PK Parameters	Increase in buprenorphine	Increase in naloxone compared to healthy
---------	---------------	---------------------------	--

Impairment		compared to healthy subjects	subjects
Moderate	C <sub>max</sub>	8%	170%
	AUC <sub>0-last</sub>	64%	218%
	Half-life	35%	165%
Severe	C <sub>max</sub>	72%	1030%
	AUC <sub>0-last</sub>	181%	1302%
	Half-life	57%	122%

The difference in magnitude of the effects on naloxone and buprenorphine are greater in subjects with severe hepatic impairment than subjects with moderate hepatic impairment, and therefore the clinical impact of these effects is likely to be greater in patients with severe hepatic impairment than in patients with moderate hepatic impairment. Buprenorphine/naloxone products should be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment [see *Warnings and Precautions (5.11)* and *Use in Specific Populations (8.6)*].

**HCV infection:** In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean C<sub>max</sub>, AUC<sub>0-last</sub>, and half-life values of buprenorphine and naloxone were not clinically significant in comparison to healthy subjects without HCV infection. No dosing adjustment is needed in patients with HCV infection.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### **Carcinogenicity**

Carcinogenicity data on SUBOXONE sublingual film are not available.

A carcinogenicity study of buprenorphine/naloxone (4:1 ratio of the free bases) was performed in Alderley Park rats. Buprenorphine/naloxone was administered in the diet at doses of approximately 7, 31, and 123 mg/kg/day for 104 weeks (estimated exposure was approximately 4, 18, and 44 times the recommended human sublingual dose of 16 mg/4 mg buprenorphine/naloxone based on buprenorphine AUC comparisons). A statistically significant increase in Leydig cell adenomas was observed in all dose groups. No other drug-related tumors were noted.

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3, and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rats, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86 week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis).

#### **Mutagenicity**

The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli*. The combination was not

clastogenic in an *in vitro* cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat.

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* “rec” assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both *in vivo* and *in vitro* incorporation of [<sup>3</sup>H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

### **Impairment of Fertility**

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m<sup>2</sup> basis) had no adverse effect on fertility.

## **16 HOW SUPPLIED / STORAGE AND HANDLING**

SUBOXONE sublingual film is supplied as an orange rectangular film with a white printed logo in child-resistant polyester/foil laminated pouches:

- NDC 12496-1202-3 (buprenorphine/naloxone 2 mg/0.5 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1204-3 (buprenorphine/naloxone 4 mg/1 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1208-3 (buprenorphine/naloxone 8 mg/2 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1212-3 (buprenorphine/naloxone 12 mg/3 mg/film; content expressed in terms of free base) - 30 films per carton

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

**Patients should be advised to store buprenorphine-containing medications safely and out of sight and reach of children.**

Rx only

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

SUBOXONE sublingual film must be administered whole. Advise patients not to cut, chew, or swallow SUBOXONE sublingual film

### Safe Use

**Before initiating treatment with SUBOXONE sublingual film, explain the points listed below to caregivers and patients. Instruct patients to read the Medication Guide each time SUBOXONE sublingual film is dispensed because new information may be available.**

- Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking SUBOXONE sublingual film. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician *[see Warnings and Precautions (5.2), Drug Interactions (7.3)]*.
- Patients should be advised that SUBOXONE sublingual film contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their films in a safe place, and to protect them from theft.
- Patients should be instructed to keep SUBOXONE sublingual film in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to SUBOXONE sublingual film, medical attention should be sought immediately.
- Patients should be advised never to give SUBOXONE sublingual film to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Patients should be advised that selling or giving away this medication is against the law.
- Patients should be cautioned that SUBOXONE sublingual film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving or operating machinery. Caution should be taken especially during drug induction and dose adjustment and until individuals are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities *[see Warnings and Precautions (5.11)]*.
- Patients should be advised not to change the dosage of SUBOXONE sublingual film without consulting their physician.
- Patients should be advised to take SUBOXONE sublingual film once a day.
- Patients should be advised that if they miss a dose of SUBOXONE they should take it as soon as they remember. If it is almost time for the next dose, they should skip the missed dose and take the next dose at the regular time.
- Patients should be informed that SUBOXONE sublingual film can cause drug dependence and that withdrawal signs and symptoms may occur when the medication is discontinued.
- Patients seeking to discontinue treatment with buprenorphine for opioid dependence should be advised to work closely with their physician on a tapering schedule and should be apprised of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.

- Patients should be cautioned that, like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory individuals [see *Warnings and Precautions (5.12)*].
- Patients should inform their physician if any other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used [see *Drug Interactions (7.1, 7.2 and 7.3)*].
- Advise women that if they are pregnant while being treated with SUBOXONE, the baby may have signs of withdrawal at birth and that withdrawal is treatable [see *Warnings and Precautions (5.5), Specific Populations (8.1)*].
- Advise women who are breastfeeding to monitor the infant for drowsiness and difficulty breathing [see *Use in Specific Populations (8.3)*].
- Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with SUBOXONE sublingual film.
- Refer to the Medication Guide for additional information regarding the counseling information.

#### **Disposal of Unused SUBOXONE Sublingual Films**

Unused SUBOXONE sublingual films should be disposed of as soon as they are no longer needed. Unused films should be flushed down the toilet.

Manufactured for Indivior Inc.  
Richmond, VA 23235 by:  
MonoSol Rx, LLC,  
Warren, NJ 07059

Distributed by:  
Indivior Inc.  
Richmond, VA 23235

## **Appendix 8 Study Drug Preparation, Administration, and Depot Removal Instructions**

### **RBP-6000 PREPARATION AND DOSING PROCEDURE**

- **100 MG BUPRENORPHINE**
- **300 MG BUPRENORPHINE**

**IMPORTANT:** Only qualified study personnel can prepare the study drug. Protective gloves (latex or nitrile) should be worn when preparing and dosing RBP-6000. Remove the product from the refrigerator at least 15 minutes before use to allow the product to reach room temperature before dosing. Product may be left at room temperature up to 8 hours prior to use. If product is not used that day it should be marked appropriately.

### **FOLLOW THE INSTRUCTIONS AS DIRECTED TO ENSURE PROPER DOSING**

#### **Preparation of the Product Prior to Administration:**

The following components will be used in the preparation of RBP-6000:

- One sealed foil pouch containing a syringe pre-filled with RBP-6000 and an oxygen absorber pack.
  - One sterile 19-gauge, 1 inch hypodermic safety needle
1. On a clean field, open the foil pouch and remove the contents. Discard the oxygen absorber pack. The pouch must be retained for accountability.
  2. Un-cap the pre-filled RBP-6000 syringe and attach the safety needle cartridge by pushing in and turning the needle until it is finger tight. Do not strip the threaded fitting by over-tightening the needle. Position the sheath at 90 degrees to the needle. Pull off the needle cartridge cover. More complete documentation on the usage of the SurGuard2 safety needle can be found in the included instruction sheet.
  3. While holding the syringe vertically with the tip upwards, expel air bubbles by stroking the plunger up and down.
  4. The product is now ready for administration. Carefully recap the needle.

#### **Administration Procedure:**

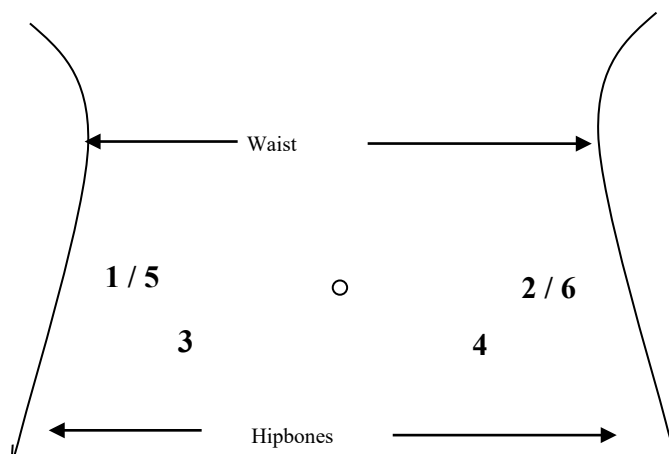
**IMPORTANT: Once prepared (removed from foil pouch), the product must be administered within a maximum of 30 minutes.**

Choose an injection site below the waist but above the hip bone; from where the body curves at the side to about 2 inches from the middle of the abdomen with adequate amounts of subcutaneous tissue that does not have excessive pigment, nodules, lesions, or hair. Since you can vary the injection site with a subcutaneous injection, choose an area that has not recently been used.

Possible injection site locations and an injection rotation pattern are shown in Figure 4. Injections should be started based on where the last injection in RB-US-13-0001 was given for roll-over subjects.



**Figure 4          Injection Locations**



1. Cleanse the injection-site area with an alcohol swab.
2. Using the thumb and forefinger of your non-dominant hand, grab and bunch the area of skin around the injection site.
3. Using your dominant hand, insert approximately half the needle length quickly. The approximate angle you use will depend on the amount and fullness of the subcutaneous tissue and the length of the needle.
4. After the needle is inserted, release the skin with your nondominant hand.
5. Pull back on the plunger to check for blood. If blood is present in the syringe, do not inject. Withdraw the needle and discard all components safely in an appropriate biohazard container. Repeat the “Preparation of the Product Prior to **Administration**” procedures and the “**Administration Procedure**” using a different abdominal injection site with another syringe of RBP-6000 and associated components.
6. Inject the product using a slow, steady push. Press down on the plunger until the syringe is empty.
7. Withdraw the needle at the same angle used for insertion. Do not rub the injection area. If there is bleeding, apply minimal pressure with a gauze pad or bandage. Engage the safety sheath on the needle as per the SurGuard2 needle instructions.
8. Discard all components safely in an appropriate biohazard container.

## PROCEDURE FOR REMOVAL OF THE RBP-6000 DEPOT

In the event of an emergency or if a subject withdraws or is withdrawn within the first 14 days of receiving an injection of RBP-6000, subjects may have the option to have the depot surgically removed by a physician delegated to perform surgery. The medically responsible physician should carefully discuss this option with subjects given the use of ATRIGEL Delivery System and the feasibility of extracting the depot.

The following surgical procedure should be followed:

1. Palpate the depot and surrounding area to confirm its exact location.
2. Cleanse the area with an antiseptic solution (e.g., Betadine).
3. Infiltrate the area with a local anesthesia (e.g., Lidocaine 1% or a lidocaine/adrenaline [epinephrine] mixture) and wait for it to take effect.
4. Cover the area with a sterile drape.
5. Incise the skin up to the subcutaneous tissues using a scalpel.
6. Using blunt and sharp dissection, identify the plane between the depot and surrounding subcutaneous tissues. Once the plane is identified, separate the superficial 25% of the circumference of the depot with blunt dissection.
7. Gently lift the incised ellipse of skin and depot with forceps.
8. Once the depot is removed, ensure hemostasis, and close the skin with non-absorbable sutures.
9. The extracted RBP-6000 depot will be disposed of into an appropriate, secure biohazard container per the SOP at the study site.

## Appendix 9 Prohibited Cytochrome P450 Inhibitors and Inducers

The following medications are prohibited during the study:

Cytochrome P450 3A4 Inhibitors		Cytochrome P450 3A4 Inducers	Cytochrome P450 2C8 Inhibitors	Cytochrome P450 2C8 Inducers
Amiodarone	Ketoconazole	Barbiturates	Gemfibrozil	Rifampicin
Amprenavir	Metronidazole	Carbamazepine	Trimethoprim	
Aprepitant	Mibefradil	Dexamethasone	Glitazones	
Chloramphenicol	Miconazole	Efavirenz	Montelukast	
Cimetidine	Mifepristone	Ethosuximide	Quercetin	
Ciprofloxacin	Nefazodone	Glucocorticoids		
Clarithromycin	Nelfinavir	Glutethimide		
Clotrimazole	Nicardipine	Modafinil		
Cyclosporine	Norfloxacin	Nevirapine		
Delavirdine	Norfluoxetine	Oxcarbazepine		
Diethyl- dithiocarbamate	Propofol	Phenobarbital		
Diltiazem	Quinine	Phenytoin		
Ethinyl estradiol	Ritonavir	Pioglitazone		
Erythromycin	Saquinavir	Primidone		
Fluconazole	Sertraline	Rifabutin		
Fluoxetine	Starfruit	Rifampin		
Fluvoxamine	Telithromycin	Hypericum perforatum		
Gestodene	Troleandomycin	Sulfadimidine		
Grapefruit juice	Verapamil	Sulfinpyrazone		
Imatinib	Voriconazole	Troglitazone		
Indinavir	Zafirlukast	Troleandomycin		
Itraconazole				

Source: <http://medicine.iupui.edu/clinpharm/ddis/clinical-table/>

## Appendix 10 Columbia Suicide Severity Rating Scale (eC-SSRS) -- Baseline/Screening Version

<b>SUICIDAL IDEATION</b>		<b>Lifetime: Time He/She Felt Most Suicidal</b>	<b>Past ___ Months</b>
<p><i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i></p>			
<p><b>1. Wish to be Dead</b> Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i></p> <p>If yes, describe:</p>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<p><b>2. Non-Specific Active Suicidal Thoughts</b> General non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i></p> <p>If yes, describe:</p>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<p><b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b> Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it." <i>Have you been thinking about how you might do this?</i></p> <p>If yes, describe:</p>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<p><b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b> Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i></p> <p>If yes, describe:</p>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<p><b>5. Active Suicidal Ideation with Specific Plan and Intent</b> Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i></p> <p>If yes, describe:</p>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>INTENSITY OF IDEATION</b>			
<p><i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.</i></p> <p><u>Lifetime</u> - <b>Most Severe Ideation:</b> _____ Type # (1-5) Description of Ideation</p> <p><u>Past X Months</u> - <b>Most Severe Ideation:</b> _____ Type # (1-5) Description of Ideation</p>		Most Severe	Most Severe
<p><b>Frequency</b> <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day</p>		_____	_____
<p><b>Duration</b> <i>When you have the thoughts how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time</p>		_____	_____
<p><b>Controllability</b> <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (6) Does not attempt to control thoughts</p>		_____	_____
<p><b>Deterrents</b> <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (6) Does not apply</p>		_____	_____
<p><b>Reasons for Ideation</b> <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (6) Does not apply</p>		_____	_____

Version 1/14/09

SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)		Lifetime	Past Years
<b>Actual Attempt:</b> A potentially self-injurious act committed with at least some wish to die, <i>as a result of fact</i> . Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <i>any</i> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <b>There does not have to be any injury or harm</b> , just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. <b>Have you made a suicide attempt?</b> <b>Have you done anything to harm yourself?</b> <b>Have you done anything dangerous where you could have died?</b> <i>What did you do?</i> <i>Did you _____ as a way to end your life?</i> <i>Did you want to die (even a little) when you _____?</i> <i>Were you trying to end your life when you _____?</i> <i>Or Did you think it was possible you could have died from _____?</i> <b>Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?</b> (Self-Injurious Behavior without suicidal intent) If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of Attempts _____	Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of Attempts _____
<b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>Interrupted Attempt:</b> When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act ( <i>if not for that, actual attempt would have occurred</i> ). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. <b>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?</b> If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of interrupted _____	Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of interrupted _____
<b>Aborted Attempt:</b> When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. <b>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?</b> If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of aborted _____	Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of aborted _____
<b>Preparatory Acts or Behavior:</b> Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). <b>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?</b> If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>Suicidal Behavior:</b> Suicidal behavior was present during the assessment period?		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>Answer for Actual Attempts Only</b>		Most Recent Attempt Date:	Initial/First Attempt Date:
<b>Actual Lethality/Medical Damage:</b> 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death		Enter Code  _____	Enter Code  _____
<b>Potential Lethality: Only Answer if Actual Lethality=0</b> Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).  0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care		Enter Code  _____	Enter Code  _____

## Appendix 11 Columbia Suicide Severity Rating Scale (eC-SSRS) -- Since Last Visit Version

<b>SUICIDAL IDEATION</b>	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
<b>1. Wish to be Dead</b> Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>2. Non-Specific Active Suicidal Thoughts</b> General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b> Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it." <i>Have you been thinking about how you might do this?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b> Thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>5. Active Suicidal Ideation with Specific Plan and Intent</b> Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>INTENSITY OF IDEATION</b>	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).  Most Severe Ideation: _____ <div style="display: flex; justify-content: space-between;"> <span>Type # (1-5)</span> <span>Description of Ideation</span> </div>	Most Severe
<b>Frequency</b> <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	_____
<b>Duration</b> <i>When you have the thoughts, how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	_____
<b>Controllability</b> <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (6) Does not attempt to control thoughts	_____
<b>Deterrents</b> <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (6) Does not apply	_____
<b>Reasons for Ideation</b> <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (6) Does not apply	_____

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## Appendix 12 Clinical Opiate Withdrawal Scale (COWS)

For each item, mark the choice that best describes the subject's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

**1. Resting Pulse Rate:** *Measured after patient is sitting or lying for one minute.*

- \_\_\_\_\_ beats/min
- ☐ 0 - Pulse rate 80 or below
  - ☐ 1 - Pulse rate 81 - 100
  - ☐ 2 - Pulse rate 101 - 120
  - ☐ 4 - Pulse rate greater than 120

**2. GI upset:** *Over last 1/2 hour.*

- ☐ 0 - No GI symptoms
- ☐ 1 - Stomach cramps
- ☐ 2 - Nausea or loose stool
- ☐ 3 - Vomiting or diarrhea
- ☐ 5 - Multiple episodes of diarrhea or vomiting

**3. Sweating:** *Over past 1/2 hour not accounted for by room temperature or patient activity.*

- ☐ 0 - No report of chills or flushing
- ☐ 1 - Subjective report of chills or flushing
- ☐ 2 - Flushed or observable moistness on face
- ☐ 3 - Beads of sweat on brow or face
- ☐ 4 - Sweat streaming off face

**4. Tremor:** *Observation of outstretched hands.*

- ☐ 0 - No tremor
- ☐ 1 - Tremor can be felt, but not observed
- ☐ 2 - Slight tremor observable
- ☐ 4 - Gross tremor or muscle twitching

**5. Restlessness:** *Observation during assessment.*

- ☐ 0 - Able to sit still
- ☐ 1 - Reports difficulty sitting still, but is able to do so
- ☐ 3 - Frequent shifting or extraneous movements of legs/arms
- ☐ 5 - Unable to sit still for more than a few seconds

**6. Yawning:** *Observation during assessment.*

- ☐ 0 - No yawning
- ☐ 1 - Yawning once or twice during assessment
- ☐ 2 - Yawning three or more times during assessment
- ☐ 4 - Yawning several times/minute



**7. Pupil Size:**

- ☐ 0 - Pupils pinned or normal size for room light
- ☐ 1 - Pupils possibly larger than normal for room light
- ☐ 2 - Pupils moderately dilated
- ☐ 5 - Pupils so dilated that only the rim of the iris is visible

**8. Anxiety or Irritability:**

- ☐ 0 - None
- ☐ 1 - Patient reports increasing irritability or anxiousness
- ☐ 2 - Patient obviously irritable or anxious
- ☐ 4 - Patient so irritable or anxious that participation in the assessment is difficult

**9. Bone or Joint aches:**

- If patient was having pain previously, only the additional component attributed to opiate withdrawal is scored.*
- ☐ 0 - Not present
  - ☐ 1 - Mild diffuse discomfort
  - ☐ 2 - Patient reports severe diffuse aching of joints/muscle
  - ☐ 4 - Patient is rubbing joints or muscles and is unable to sit still because of discomfort

**10. Gooseflesh skin:**

- ☐ 0 - Skin is smooth
- ☐ 3 - Piloerection of skin can be felt or hairs standing up on arms
- ☐ 5 - Prominent piloerection

**11. Runny nose or tearing:**

- Not accounted for by cold symptoms or allergies.*
- ☐ 0 - Not present
  - ☐ 1 - Nasal stuffiness or unusually moist eyes
  - ☐ 2 - Nose running or tearing
  - ☐ 4 - Nose constantly running or tears streaming down cheeks

**TOTAL SCORE (sum of all 11 items):**

--	--

*Score Interpretation: 5 - 12= Mild, 13 - 24= Moderate, 25 - 36=Moderately Severe, More than 36= Severe Withdrawal*

## Appendix 13 Subjective Opiate Withdrawal Scale (SOWS)

		PLEASE SCORE EACH OF THE 16 ITEMS BELOW ACCORDING TO HOW YOU FEEL NOW (CIRCLE ONE NUMBER)				
	SYMPTOM	NOT AT ALL	A LITTLE	MODERATELY	QUITE A BIT	EXTREMELY
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

Modified from : Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubenstein KJ, Kanof PD (1987). Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse* 13:293-308.

## **Appendix 14      Opioid Craving Visual Analog Scale (Opioid Craving VAS)**

No craving \_\_\_\_\_ Strongest craving ever  
100 mm scale

## Appendix 15 Injection Site Grading Scale

<b>Injection Site Reactions</b>	<b>None (Grade 0)</b>	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>	<b>Potentially Life Threatening (Grade 4)</b>
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 (ER) visit or hospitalization
Tenderness	None	Mild discomfort to touch.	Discomfort with movement.	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness* (quantitative)	None	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration **	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 ** (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

\* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

\*\* Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Modified from:

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, September 2007. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. [pdf] Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf>. Accessed 14 April 2015.

## **Appendix 16    Injection Site Pain Visual Analog Scale (Injection Site Pain VAS)**

How would you rate your injection site pain today?

No \_\_\_\_\_ Pain as bad  
Pain \_\_\_\_\_ as it could be

Please answer the following question by checking the box with either a “Yes” or “No”:  
Are you currently experiencing any burning or stinging at the injection site?

YES ☐

NO ☐

## Appendix 17 Timeline Followback (TLFB) Interview

TIMELINE FOLLOWBACK INTERVIEW											Ethanol
Study Day	Date (mm / dd / yyyy)	Opioids	Methadone	Bup	Cocaine	Barbit.	Benzos	Amp/Meth	PCP	Completed By: (initials/date)	
	□□ / □□ / 20□□	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use		<input type="radio"/> Use <input type="radio"/> No Use
	□□ / □□ / 20□□	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use		<input type="radio"/> Use <input type="radio"/> No Use
	□□ / □□ / 20□□	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use		<input type="radio"/> Use <input type="radio"/> No Use
	□□ / □□ / 20□□	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use		<input type="radio"/> Use <input type="radio"/> No Use
	□□ / □□ / 20□□	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use		<input type="radio"/> Use <input type="radio"/> No Use
	□□ / □□ / 20□□	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use		<input type="radio"/> Use <input type="radio"/> No Use
	□□ / □□ / 20□□	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use		<input type="radio"/> Use <input type="radio"/> No Use
	□□ / □□ / 20□□	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use		<input type="radio"/> Use <input type="radio"/> No Use
	□□ / □□ / 20□□	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use	<input type="radio"/> Use <input type="radio"/> No Use		<input type="radio"/> Use <input type="radio"/> No Use

## Appendix 18 Euro QoL EQ-5D-5L Health Questionnaire

### EQ-5D-5L Health Questionnaire

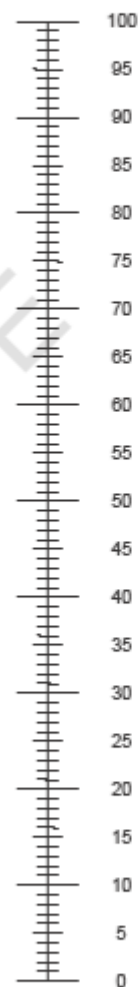
Under each heading, please check the ONE box that best describes your health TODAY

<b>MOBILITY</b>	
I have no problems walking	<input type="checkbox"/>
I have slight problems walking	<input type="checkbox"/>
I have moderate problems walking	<input type="checkbox"/>
I have severe problems walking	<input type="checkbox"/>
I am unable to walk	<input type="checkbox"/>
<b>SELF-CARE</b>	
I have no problems washing or dressing myself	<input type="checkbox"/>
I have slight problems washing or dressing myself	<input type="checkbox"/>
I have moderate problems washing or dressing myself	<input type="checkbox"/>
I have severe problems washing or dressing myself	<input type="checkbox"/>
I am unable to wash or dress myself	<input type="checkbox"/>
<b>USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)</b>	
I have no problems doing my usual activities	<input type="checkbox"/>
I have slight problems doing my usual activities	<input type="checkbox"/>
I have moderate problems doing my usual activities	<input type="checkbox"/>
I have severe problems doing my usual activities	<input type="checkbox"/>
I am unable to do my usual activities	<input type="checkbox"/>
<b>PAIN/DISCOMFORT</b>	
I have no pain or discomfort	<input type="checkbox"/>
I have slight pain or discomfort	<input type="checkbox"/>
I have moderate pain or discomfort	<input type="checkbox"/>
I have severe pain or discomfort	<input type="checkbox"/>
I have extreme pain or discomfort	<input type="checkbox"/>
<b>ANXIETY/DEPRESSION</b>	
I am not anxious or depressed	<input type="checkbox"/>
I am slightly anxious or depressed	<input type="checkbox"/>
I am moderately anxious or depressed	<input type="checkbox"/>
I am severely anxious or depressed	<input type="checkbox"/>
I am extremely anxious or depressed	<input type="checkbox"/>

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.  
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health  
you can imagine



The worst health  
you can imagine

USA (English) © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

Hendman M, Gudex C, Lloyd A, Jansen ME, Kind R, Parkin D, Rosner G, Badia X.  
Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L).  
Quality of Life Research (accepted for publication).



## Appendix 19 Short Form (36) Health Survey v2

### The SF-36v2™ Health Survey

#### Instructions for Completing the Questionnaire

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

#### EXAMPLE

**This is for your review.** Do not answer this question. The questionnaire begins with the section *Your Health in General* below.

For each question you will be asked to fill in a bubble in each line:

1. How strongly do you agree or disagree with each of the following statements?

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
a) I enjoy listening to music.	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b) I enjoy reading magazines.	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Please begin answering the questions now.

### Your Health in General

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>

GH01

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>

HT

**Please turn the page and continue.**

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all	
a) <b>Vigorous activities</b> , such as running, lifting heavy objects, participating in strenuous sports	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	PF01
b) <b>Moderate activities</b> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	PF02
c) Lifting or carrying groceries	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	PF03
d) Climbing <b>several</b> flights of stairs	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	PF04
e) Climbing <b>one</b> flight of stairs	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	PF05
f) Bending, kneeling, or stooping	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	PF06
g) Walking <b>more than a mile</b>	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	PF07
h) Walking <b>several hundred yards</b>	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	PF08
i) Walking <b>one hundred yards</b>	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	PF09
j) Bathing or dressing yourself	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	PF10

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
a) Cut down on the <b>amount of time</b> you spent on work or other activities	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	RP01
b) <b>Accomplished less</b> than you would like	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	RP02
c) Were limited in the <b>kind of work</b> or other activities	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	RP03
d) Had <b>difficulty</b> performing the work or other activities (for example, it took extra effort)	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	RP04

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
a) Cut down on the <b>amount of time</b> you spent on work or other activities	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	RE01
b) <b>Accomplished less</b> than you would like	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	RE02
c) Did work or other activities <b>less carefully</b> than usual	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	RE03

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely	
<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	SF01

7. How much **bodily pain** have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe	
<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	<input type="radio"/> <sub>6</sub>	BP01

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely	
<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	BP02

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
a) did you feel full of life?	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	VT01
b) have you been very nervous?	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	MH01
c) have you felt so down in the dumps that nothing could cheer you up?	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	MH02
d) have you felt calm and peaceful?	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	MH03
e) did you have a lot of energy?	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	VT02
f) have you felt downhearted and depressed?	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	MH04
g) did you feel worn out?	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	VT03
h) have you been happy?	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	MH05
i) did you feel tired?	<input type="radio"/> <sub>1</sub>	<input type="radio"/> <sub>2</sub>	<input type="radio"/> <sub>3</sub>	<input type="radio"/> <sub>4</sub>	<input type="radio"/> <sub>5</sub>	VT04

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time	
<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	SF02

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
a) I seem to get sick a little easier than other people	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	GH02
b) I am as healthy as anybody I know	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	GH03
c) I expect my health to get worse	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	GH04
d) My health is excellent	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5	GH05

## **Appendix 20      Medication Satisfaction Questionnaire**

Overall, how satisfied are you with your current opioid dependence medication?

- 1 = extremely dissatisfied
- 2 = very dissatisfied
- 3 = somewhat dissatisfied
- 4 = neither satisfied nor dissatisfied
- 5 = somewhat satisfied
- 6 = very satisfied
- 7 = extremely satisfied

## Appendix 21 Health Care Resource Utilization Questionnaire

HEALTH INSURANCE				
Primary Health Insurance (Please check all that apply)		<input type="checkbox"/> Commercial (for example, Blue Cross Blue Shield, Aetna, Humana, United, Cigna) <input type="checkbox"/> Medicare <input type="checkbox"/> Medicaid <input type="checkbox"/> Veterans Affairs <input type="checkbox"/> Workers compensation <input type="checkbox"/> Other insurance <input type="checkbox"/> Self-pay / Out of pocket/No insurance		
INPATIENT ADMISSIONS				
<ul style="list-style-type: none"> <li>Please list in the table below all inpatient admissions <b>in the past 30 days</b>. If patient is currently hospitalized, please check the box in the "Ongoing" column.</li> <li>If patient has had no previous hospitalizations <b>in the past 30 days</b>, please check the appropriate box below.</li> </ul>				
<input type="checkbox"/> No hospitalizations since the last study visit				
	Admission Date (dd / mmm / yyyy)	Discharge Date (dd / mmm / yyyy)	Ongoing?	Type of Admission
1.	__ / __ / __	__ / __ / __	<input type="checkbox"/>	<input type="checkbox"/> Medical <input type="checkbox"/> Surgical <input type="checkbox"/> Psychiatric <input type="checkbox"/> Other
2.	__ / __ / __	__ / __ / __	<input type="checkbox"/>	<input type="checkbox"/> Medical <input type="checkbox"/> Surgical <input type="checkbox"/> Psychiatric <input type="checkbox"/> Other
3.	__ / __ / __	__ / __ / __	<input type="checkbox"/>	<input type="checkbox"/> Medical <input type="checkbox"/> Surgical <input type="checkbox"/> Psychiatric <input type="checkbox"/> Other

### EMERGENCY ROOM VISITS

- Please list how many times the patient has been to the Emergency Room **in the past 30 days**.

Type of Problem	Number of Visits
Substance abuse-related	<input type="text"/> <input type="text"/> visits
Other medical problems	<input type="text"/> <input type="text"/> visits

### OUTPATIENT SERVICES

- Please list how many times the patient has seen 1 of the following health professionals **in the past 30 days**. The outpatient services captured on this questionnaire are ones conducted outside the study

Health Professional	Number of Visits
General practitioner / Internist	<input type="text"/> <input type="text"/> visits
Addiction Medicine Specialist	<input type="text"/> <input type="text"/> visits
Therapist / Counselor	<input type="text"/> <input type="text"/> visits
Other: Specialist	<input type="text"/> <input type="text"/> visits
Other: Non-Specialist	<input type="text"/> <input type="text"/> visits

## Appendix 22 Treatment Effectiveness Assessment (TEA)

Treatment Effectiveness Assessment (TEA)																																
<p>The TEA asks you to express the extent of changes for the better from your involvement in the program to this point (or how things are if it's your first TEA or baseline) in four areas: substance use, health, lifestyle, and community. For each area, think about how things have become better and circle the results on the scale below: the more you have improved, the higher the number – from 1 (not better at all) to 10 (very much better). In each area write down the one or two changes most important to you in the Remarks section. Feel free to use the back of this page to add details, explain remarks, and make comments.</p>																																
<p><b>Substance use:</b> How much better are you with drug and alcohol use? Consider the frequency and amount of use, money spent on drugs, amount of drug craving, time spent being loaded, being sick, in trouble and in other drug-using activities, etc.</p>																																
<table border="0"> <tr> <td colspan="4">None or not much</td> <td colspan="4">Better</td> <td colspan="3">Much better</td> </tr> <tr> <td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td></td> </tr> </table>											None or not much				Better				Much better			1	2	3	4	5	6	7	8	9	10	
None or not much				Better				Much better																								
1	2	3	4	5	6	7	8	9	10																							
Remarks:																																
<p><b>Health:</b> Has your health improved? In what way and how much? Think about your physical and mental health: Are you eating and sleeping properly, exercising, taking care of health problems or dental problems, feeling better about yourself, etc?</p>																																
<table border="0"> <tr> <td colspan="4">None or not much</td> <td colspan="4">Better</td> <td colspan="3">Much better</td> </tr> <tr> <td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td></td> </tr> </table>											None or not much				Better				Much better			1	2	3	4	5	6	7	8	9	10	
None or not much				Better				Much better																								
1	2	3	4	5	6	7	8	9	10																							
Remarks:																																
<p><b>Lifestyle:</b> How much better are you in taking care of personal responsibilities? Think about your living conditions, family situation, employment, relationships: Are you paying your bills? Following through with your personal or professional commitments?</p>																																
<table border="0"> <tr> <td colspan="4">None or not much</td> <td colspan="4">Better</td> <td colspan="3">Much better</td> </tr> <tr> <td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td></td> </tr> </table>											None or not much				Better				Much better			1	2	3	4	5	6	7	8	9	10	
None or not much				Better				Much better																								
1	2	3	4	5	6	7	8	9	10																							
Remarks:																																
<p><b>Community:</b> Are you a better member of the community? Think about things like obeying laws and meeting your responsibilities to society: Do your actions have positive or negative impacts on other people?</p>																																
<table border="0"> <tr> <td colspan="4">No or not much</td> <td colspan="4">Better</td> <td colspan="3">Much better</td> </tr> <tr> <td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td></td> </tr> </table>											No or not much				Better				Much better			1	2	3	4	5	6	7	8	9	10	
No or not much				Better				Much better																								
1	2	3	4	5	6	7	8	9	10																							
Remarks:																																
<p>Name: _____ Date: _____ First TEA?: [ ]</p>																																



## Appendix 23      Addiction Severity Index (ASI) Lite

<b>CTN Addiction Severity Index Lite CF</b>				Version# <b>1</b>	Approved 10/24/00 Page 1 of 16
Protocol Number:		Serial Number:		Form #	
[ ][ ][ ][ ] - [ ][ ][ ][ ] - [ ][ ][ ][ ][ ]		[ ][ ][ ][ ][ ]		2 9 1	
Node:	Site: (G3)	Name Code:	ID Number: (G1)	Date of Assessment: (mm/dd/yyyy) (G5)	
0 6	[ ][ ][ ][ ]	[ ][ ][ ][ ]	[ ][ ][ ][ ][ ]	[ ][ ] / [ ][ ] / [ ][ ][ ][ ]	
<b>Phase:</b> <input type="radio"/> Screening <input type="radio"/> Active <input type="radio"/> Follow-up1 <input type="radio"/> Follow-up2 <input type="radio"/> Follow-up3		<b>CQI Codes:</b> Blank-No errors 01-Pt unavailable 10-Data collector error 11-Pt unable/unwilling to answer		<b>CQI:</b> [ ][ ] <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	
<b>CQI Comments:</b> <input type="radio"/> Entire form <input type="radio"/> Question#(s): <b>QA Corrections:</b> <input type="radio"/> QA1 <input type="radio"/> QA2 <input type="radio"/> QA3 <input type="radio"/> QA4		<b>Study Day:</b> [ ][ ][ ]		<b>Form Completed By:</b> [ ][ ][ ] (G11)	
<b>Note: See page 16 for instructions and codes</b>					

### GENERAL INFORMATION

G4. Date of admission:

	/		/				
(MM)		(DD)		(YYYY)			

- G8. Class:
- ☐ 1-Intake
  - ☐ 2-Follow-up

- G9. Contact code:
- ☐ 1-InPerson
  - ☐ 2-Telephone(IntakeASImustbeinperson)
  - ☐ 3-Mail

- G10. Gender:
- ☐ 1-Male
  - ☐ 2-Female

- G12. Special:
- ☐ 1-Patientterminated
  - ☐ 2-Patientrefused
  - ☐ 3-Patientunabletorespond

Comments:

Please  
PRINT CLEARLY

1	2	3	4	5	6	7	8	9	0
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A	B	C	D	E	F	G	H	I	J	K	L	M
N	O	P	Q	R	S	T	U	V	W	X	Y	Z

Confidential

**GENERAL INFORMATION**  
(continued)

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SerialNumber:

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22325

<b>Site:</b>	<b>Name Code:</b>	<b>ID Number:</b>	<b>Date of Assessment:</b> (mm/dd/yyyy)																							
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G14. How long have you lived at your current address?

<table border="1"><tr><td></td><td></td></tr></table>			/	<table border="1"><tr><td></td><td></td></tr></table>		
A-Yrs.		B-Mos.				

G16. Date of birth:

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(MM)		(DD)		(YYYY)								

G17. Of what race do you consider yourself?

- ☐ 1-White(NotHispanic)  
☐ 2-Black(NotHispanic)  
☐ 3-AmericanIndian  
☐ 4-AlaskanNative  
☐ 5-Asian/Pacific  
☐ 6-Hispanic-Mexican  
☐ 7-Hispanic-PuertoRican  
☐ 8-Hispanic-Cuban  
☐ 9-OtherHispanic

G18. Do you have a religious preference?

- ☐ 1-Protestant  
☐ 2-Catholic  
☐ 3-Jewish  
☐ 4-Islamic  
☐ 5-Other: \_\_\_\_\_  
☐ 6-None

G19. Have you been in a controlled environment in the past 30 days?

- ☐ 1-No  
☐ 2-Jail  
☐ 3-AlcoholorDrugTreat.  
☐ 4-MedicalTreatment  
☐ 5-PsychiatricTreatment  
☐ 6-Other: \_\_\_\_\_  
• A place, theoretically, without access to drugs/alcohol.

G20. How many days?

--	--

- "NN" if question G19 is "No". Refers to total number of days detained in the past 30 days.

Comments:

Please  
PRINT CLEARLY

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A	B	C	D	E	F	G	H	I	J	K	L	M
N	O	P	Q	R	S	T	U	V	W	X	Y	Z

## MEDICAL STATUS

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SerialNumber:

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22325

Site:	Name Code:	ID Number:	Date of Assessment:	(mm/dd/yyyy)																									
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- \* M1. How many times in your life have you been hospitalized for medical problems? 

--	--
- Include O.D.'s & D.T.'s. Exclude detox, alcohol/drug, psychiatric treatment and childbirth (if no complications). Enter the number of **overnight** hospitalizations for medical problems.
- M3. Do you have any chronic medical problems which continue to interfere with your life? ☐ 1-Yes ☐ 0-No
- If "Yes", specify in comments.
  - A chronic medical condition is a serious physical condition that requires regular care, (i.e., medication, dietary restriction) preventing full advantage of their abilities.
- M4. Are you taking any prescribed medication on a regular basis for a physical problem? ☐ 1-Yes ☐ 0-No
- If "Yes", specify in comments.
  - Medication prescribed by a M.D. for medical conditions; **not psychiatric medicines**. Include medicines prescribed whether or not the patient is currently taking them. The intent is to verify chronic medical problems
- M5. Do you receive a pension for a physical disability? ☐ 1-Yes ☐ 0-No
- If "Yes", specify in comments.
  - Include Worker's Compensation, exclude psychiatric disability.
- M6. How many days have you experienced medical problems in the past 30 days? 

--	--
- Do not include ailments directly caused by drugs/alcohol.
  - Include flu, colds, etc. Include serious ailments related to drugs/alcohol, which would continue even if the patient were abstinent (e.g., cirrhosis of the liver, abscesses from needles, etc.).

For questions M7 & M8, please ask patient to use the Patient's Rating Scale.

- M7. How troubled or bothered have you been by these medical problems in the past 30 days? ☐ ☐ ☐ ☐ ☐
- Restrict response to problem days of question M6.
- M8. How important to you *now* is treatment for these medical problems? ☐ ☐ ☐ ☐ ☐
- Refers to the need for **new** or **additional** medical treatment by the patient.

### CONFIDENCE RATINGS

Is the above information **significantly** distorted by:

- M10. Patient's misrepresentation? ☐ 1-Yes ☐ 0-No
- M11. Patient's inability to understand? ☐ 1-Yes ☐ 0-No

Comments:

Please  
PRINT CLEARLY

1	2	3	4	5	6	7	8	9	0
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A	B	C	D	E	F	G	H	I	J	K	L	M
N	O	P	Q	R	S	T	U	V	W	X	Y	Z



## EMPLOYMENT/SUPPORT STATUS

Approved 10/24/00  
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SerialNumber:

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Site:	Name Code:	ID Number:	Date of Assessment:	(mm/dd/yyyy)

- \* E1. Education completed     
• GED = 12 years, note in comments  
• Include formal education only.  
A-Yrs. B-Mos.

- \* E2. Training or technical education completed   
• Formal/organized training only. For military training, only include training that can be used in civilian life, i.e., electronics or computers.  
Mos.

- E4. Do you have a valid driver's license? ☐ 1-Yes ☐ 0-No  
• Valid license; not suspended/revoked.

- E5. Do you have an automobile available for use? ☐ 1-Yes ☐ 0-No  
• If answer to E4 is "No", then E5 must be "No". Does not require ownership, only requires availability on a regular basis.

- E6. How long was your longest full time job?    
• Full time=35+ hours weekly; does not necessarily mean most recent job.  
A-Yrs. B-Mos.

- E7. Usual (or last) occupation   
See Hollingshead categories on page 16  
(Specify in detail)

- E9. Does someone contribute the majority of your support? ☐ 1-Yes ☐ 0-No

- E10. Usual employment pattern, past three years:  
☐ 1-Full time (35+ hours) ☐ 5-Military Service  
☐ 2-Part time (reg. hrs) ☐ 6-Retired/disability  
☐ 3-Part time (irreg. hrs) ☐ 7-Unemployed  
☐ 4-Student ☐ 8-In controlled environment

- Answer should represent the *majority* of the last 3 years, not just the most recent selection. If there are equal times for more than one category, select that which best represents the more current situation.

- E11. How many days were you paid for working in the past 30 days?

- Include "under the table" work, paid sick days, and vacations.

Comments:

A	B	C	D	E	F	G	H	I	J	K	L	M
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## EMPLOYMENT/SUPPORT STATUS (continued)

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SerialNumber:

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Site:	Name Code:	ID Number:	Date of Assessment:	(mm/dd/yyyy)
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For questions E12-17: **How much money did you receive from the following sources in the past 30 days?**

- E12. Employment: \$   
 • Net or "take home" pay, include any "under the table" money.
- E13. Unemployment compensation: \$
- E14. Welfare: \$   
 • Include food stamps, transportation money provided by an agency to go to and from treatment.
- E15. Pensions, benefits, or social security: \$   
 • Include disability, pensions, retirement, veteran's benefits, SSI & workers' compensation.
- E16. Mate, family or friends: \$   
 • Money for personal expenses, (i.e., clothing), include unreliable sources of income (e.g., gambling). Record **cash** payments only, include windfalls (unexpected), money from loans, gambling, inheritance, tax returns, etc.).
- E17. Illegal: \$   
 • **Cash** obtained from drug dealing, stealing, fencing stolen goods, gambling, prostitution, etc. **Do not** attempt to convert drugs exchanged to a dollar value.
- E18. How many people depend on you for the majority of their food, shelter, etc.?   
 • Must be regularly depending on patient, do include alimony/child support, do not include the patient or self-supporting spouse, etc.
- E19. How many days have you experienced employment problems in the past 30?   
 • Include inability to find work, if they are actively looking for work, or problems with present job in which that job is jeopardized.

Comments:

For question E20-21, please ask patient to use the Patient's Rating Scale.

- E20. How troubled or bothered have you been by these employment problems in the past 30 days? ☐ ☐ ☐ ☐ ☐  
 • If the patient has been incarcerated or detained during the past 30 days, they cannot have employment problems.
- E21. How important to you *now* is counseling for these employment problems? ☐ ☐ ☐ ☐ ☐  
 • The patients rating in question E20-21 refer to question E19.  
 • Stress help in finding or preparing for a job, not giving them a job.

### CONFIDENCE RATINGS

Is the above information significantly distorted by:

- E23. Patient's misrepresentation? ☐ 1-Yes ☐ 0-No
- E24. Patient's inability to understand? ☐ 1-Yes ☐ 0-No



# ALCOHOL/DRUGS

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SerialNumber:

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**Past 30 Days** **Lifetime use**

**A-Days** **B-Years**

D1. Alcohol - (any use at all)

D2. Alcohol - (to intoxication)

Route of administration:  
1-Oral  
2-Nasal  
3-Smoking  
4-Non IV injection  
5-IV injection  
*Note the usual or most recent route. For more than one route, choose the most severe. The routes are listed from least severe to most severe.*

Comments:

D3. Heroin     ☐ Oral ☐ Non IV  
☐ Nasal ☐ IV  
☐ Smoke

D4. Methadone     ☐ Oral ☐ Non IV  
☐ Nasal ☐ IV  
☐ Smoke

D5. Other opiates/analgesics     ☐ Oral ☐ Non IV  
☐ Nasal ☐ IV  
☐ Smoke

D6. Barbiturates     ☐ Oral ☐ Non IV  
☐ Nasal ☐ IV  
☐ Smoke

D7. Other sed/hyp/tranq.     ☐ Oral ☐ Non IV  
☐ Nasal ☐ IV  
☐ Smoke

D8. Cocaine     ☐ Oral ☐ Non IV  
☐ Nasal ☐ IV  
☐ Smoke

D9. Amphetamines     ☐ Oral ☐ Non IV  
☐ Nasal ☐ IV  
☐ Smoke

D10. Cannabis     ☐ Oral ☐ Non IV  
☐ Smoke ☐ IV

D11. Hallucinogens     ☐ Oral ☐ Non IV  
☐ Nasal ☐ IV  
☐ Smoke

D12. Inhalants     ☐ Nasal

D13. More than one substance per day (including alcohol).

**SERIAL** number on this page  
should match number on page 1

A	B	C	D	E	F	G	H	I	J	K	L	M
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### Alcohol/Drugs (continued)

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SerialNumber:

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- D17. How many times have you had Alcohol DT's?  
• **Delirium Tremens (DT's):** Occur 24-48 hours after last drink, or significant decrease in alcohol intake. Characterized by shaking, severe disorientation, fever, hallucinations, they usually require medical attention.

--	--

Comments:

- \* How many times in your life have you been treated for:  
\* (D19) Alcohol abuse

--	--

- \* (D20) Drug abuse  
• Include detoxification, halfway houses, in/outpatient counseling and AA or NA (if 3+ meetings within one month period)

--	--

How many of these were detox only:

- (D21) Alcohol?

--	--

- (D22) Drugs?

• If D19="00", then question D21 is "NN"

If D20="00", then question D22 is "NN"

--	--

How much money would you say you spent during the past 30 days on:

- (D23) Alcohol

\$ 

--	--	--	--	--

- (D24) Drugs

• Only count actual money spent. What is the financial burden caused by drugs/alcohol?

\$ 

--	--	--	--	--

- (D25) How many days have you been treated in an outpatient setting for alcohol or drugs in the past 30 days?

• Include AA/NA

--	--

For questions D28-31, please ask patient to use the Patient's Rating Scale. The patient is rating the need for additional substance abuse treatment.

- (D26) How many days in the past 30 have you experienced alcohol problems?

--	--

- (D28) How troubled or bothered have you been the past 30 days by these alcohol problems? ○ ○ ○ ○ ○

- (D30) How important to you *now* is treatment for these alcohol problems? ○ ○ ○ ○ ○

- (D27) How many days in the past 30 have you experienced drug problems?

--	--

• Include only: Craving, withdrawal symptoms, disturbing effects of use, or wanting to stop and being unable to.

- (D29) How troubled or bothered have you been in the past 30 days by these drug problems? ○ ○ ○ ○ ○

- (D31) How important to you *now* is treatment for these drug problems? ○ ○ ○ ○ ○

#### CONFIDENCE RATINGS

Is the above information significantly distorted by:

- (D34) Patient's misrepresentation? ○ 1-Yes ○ 0-No  
(D35) Patient's inability to understand? ○ 1-Yes ○ 0-No

## LEGAL STATUS



22325

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SerialNumber:

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Site:	Name Code:	ID Number:	Date of Assessment:	(mm/dd/yyyy)																														
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L1. Was this admission prompted or suggested by the criminal justice system?  
☐ 1-Yes ☐ 0-No  
• judge, probation/parole officer, etc.

L2. Are you on probation or parole?  
☐ 1-Yes ☐ 0-No  
• Note duration and level in comments.

How many times in your life \* have you been arrested and charged with the following:

- \* L3. Shoplifting/vandalism 

--	--
- \* L4. Parole/probation violations 

--	--
- \* L5. Drug charges 

--	--
- \* L6. Forgery 

--	--
- \* L7. Weapons offense 

--	--
- \* L8. Burglary/larceny/B&E 

--	--
- \* L9. Robbery 

--	--
- \* L10. Assault 

--	--
- \* L11. Arson 

--	--

Include total number of counts, not just convictions. Do not include juvenile (pre-age 18) crimes, unless they were charged as an adult.

Include formal charges only.

Comments:

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# **LEGAL STATUS** (continued)

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22325

SerialNumber:

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- \* L12. Rape
- \* L13. Homicide/manslaughter
- \* L14. Prostitution
- \* L15. Contempt of court
- \* L16. Other:
- \* L17. How many of these charges resulted in convictions?  
  - If L3-16="00", then question L17="NN".
  - Do not include misdemeanor offenses from questions L18-20 below.
  - Convictions include fines, probation, incarcerations, suspended sentences, and guilty pleas.

**How many times in your life have you been charged with the following:**

- \* L18. Disorderly conduct, vagrancy, public intoxication
- \* L19. Driving while intoxicated
- \* L20. Major driving violations  
  - Moving violations: speeding, reckless driving, no license, etc.
- \* L21. How many months were you incarcerated in your life?  Mos.  
  - If incarcerated 2 weeks or more, round this up to 1 month. List total number of months incarcerated.

Comments:

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**LEGAL STATUS**  
**(continued)**

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- L24. Are you presently awaiting charges, trial or sentence? ☐ 1-Yes ☐ 0-No
- L25. What for? (If multiple charges, use most severe.)
- Refers to question L24. If more than one, choose most severe.
  - Don't include civil cases, unless a criminal offense is involved.
- ☐ 03-Shoplift ☐ 08-Burglary ☐ 13-Homicide ☐ 19-DWI
- ☐ 04-Prob. viol. ☐ 09-Robbery ☐ 14-Prostitution ☐ 20-Major driving violation
- ☐ 05-Drug ☐ 10-Assault ☐ 15-Contempt
- ☐ 06-Forgery ☐ 11-Arson ☐ 16-Other
- ☐ 07-Weapons ☐ 12-Rape ☐ 18-Disorderly conduct

- L26. How many days in the past 30 were you detained or incarcerated? 

--	--
- Include being arrested and released on the same day.

- L27. How many days in the past 30 have you engaged in illegal activities for profit? 

--	--
- Exclude simple drug possession. Include drug dealing, prostitution, selling stolen goods, etc. May be cross checked with question E17 under Employment/Family Support section.

**For questions L28 & 29, please ask patient to use the Patient's Rating Scale**

- L28. How serious do you feel your present legal problems are? ☐ ☐ ☐ ☐ ☐
- Exclude civil problems.
- L29. How important to you *now* is counseling or referral for these legal problems? ☐ ☐ ☐ ☐ ☐
- Patient is rating a need for additional referral to legal counsel for defense against criminal charges.

**CONFIDENCE RATINGS**

**Is the above information significantly distorted by:**

- L31. Patient's misrepresentation? ☐ 1-Yes ☐ 0-No
- L32. Patient's inability to understand? ☐ 1-Yes ☐ 0-No

Comments:

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FAMILY/SOCIAL RELATIONSHIPS																																																									
41616		Protocol Number:		Serial Number:		Version# <b>1</b>		Approved 10/24/00 Page 11 of 16																																																	
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<b>Phase:</b> <input type="radio"/> Screening <input type="radio"/> Active <input type="radio"/> Follow-up1 <input type="radio"/> Follow-up2 <input type="radio"/> Follow-up3		<b>CQI Codes:</b> Blank-No errors 01-Pt unavailable 10-Data collector error 11-Pt unable/unwilling to answer		<b>CQI:</b> <input type="checkbox"/> <input type="checkbox"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>		<b>CQI Comments:</b> <input type="radio"/> Entire form <input type="radio"/> Question#(s): <b>QA Corrections:</b> <input type="radio"/> QA1 <input type="radio"/> QA2 <input type="radio"/> QA3 <input type="radio"/> QA4		<b>Study Day:</b>  <b>Form Completed By:</b> 																																																	
<p><b>F1.</b> Marital Status: <input type="radio"/> 1-Married <input type="radio"/> 4-Separated <input type="radio"/> 2-Remarried <input type="radio"/> 5-Divorced <input type="radio"/> 3-Widowed <input type="radio"/> 6-Never Married</p> <p>Common-law marriage=1. Specify in comments.</p> <p><b>F3.</b> Are you satisfied with this situation? Satisfied=generally liking the situation. Refers to question F1. <input type="radio"/> 2-Yes <input type="radio"/> 0-No <input type="radio"/> 1-Indifferent</p> <p><b>* F4.</b> Usual living arrangements (past 3 yrs.): <input type="radio"/> 1-With sexual partner and children <input type="radio"/> 6-With friends <input type="radio"/> 2-With sexual partner alone <input type="radio"/> 7-Alone <input type="radio"/> 3-With children alone <input type="radio"/> 8-Controlled environment <input type="radio"/> 4-With parents <input type="radio"/> 9-No stable arrangements <input type="radio"/> 5-With family</p> <div style="border: 1px solid black; padding: 5px; margin: 5px 0;"><p>Choose arrangements most representative of the past 3 years. If there is an even split in time between these arrangements, choose the most recent arrangements.</p></div> <p><b>F6.</b> Are you satisfied with these living arrangements? <input type="radio"/> 2-Yes <input type="radio"/> 0-No <input type="radio"/> 1-Indifferent</p> <p><b>Do you live with anyone who:</b></p> <p><b>F7.</b> Has a current alcohol problem? <input type="radio"/> 1-Yes <input type="radio"/> 0-No</p> <p><b>F8.</b> Uses non-prescribed drugs? <input type="radio"/> 1-Yes <input type="radio"/> 0-No</p> <p><b>F9.</b> With whom do you spend most of your free time? If a girlfriend/boyfriend is considered as family by patient, then they must refer to them as family throughout this section, not as a friend. <input type="radio"/> 1-Family <input type="radio"/> 2-Friends <input type="radio"/> 3-Alone</p> <p><b>F10.</b> Are you satisfied with spending your free time this way? A satisfied response must indicate that the person generally likes the situation. Refers to question F9. <input type="radio"/> 2-Yes <input type="radio"/> 0-No <input type="radio"/> 1-Indifferent</p> <div style="border: 1px solid black; height: 400px; margin-top: 20px; width: 100%;"></div>																																																									
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## FAMILY/SOCIAL RELATIONSHIPS (continued)

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SerialNumber:

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Site:	Name Code:	ID Number:	Date of Assessment:	(mm/dd/yyyy)

Have you had significant periods in which you have experienced serious problems getting along with:

	A. <u>Past 30 days</u>		B. <u>In your life</u>
F18. Mother	<input type="radio"/> 1-Yes <input type="radio"/> 0-No		<input type="radio"/> 1-Yes <input type="radio"/> 0-No
F19. Father	<input type="radio"/> 1-Yes <input type="radio"/> 0-No		<input type="radio"/> 1-Yes <input type="radio"/> 0-No
F20. Brothers/sisters	<input type="radio"/> 1-Yes <input type="radio"/> 0-No		<input type="radio"/> 1-Yes <input type="radio"/> 0-No
F21. Sexual partner/spouse	<input type="radio"/> 1-Yes <input type="radio"/> 0-No		<input type="radio"/> 1-Yes <input type="radio"/> 0-No
F22. Children	<input type="radio"/> 1-Yes <input type="radio"/> 0-No		<input type="radio"/> 1-Yes <input type="radio"/> 0-No
F23. Other significant family: (specify) <span style="border: 1px solid black; display: inline-block; width: 100px; height: 15px; vertical-align: middle;"></span>	<input type="radio"/> 1-Yes <input type="radio"/> 0-No		<input type="radio"/> 1-Yes <input type="radio"/> 0-No
F24. Close friends	<input type="radio"/> 1-Yes <input type="radio"/> 0-No		<input type="radio"/> 1-Yes <input type="radio"/> 0-No
F25. Neighbors	<input type="radio"/> 1-Yes <input type="radio"/> 0-No		<input type="radio"/> 1-Yes <input type="radio"/> 0-No
F26. Co-workers	<input type="radio"/> 1-Yes <input type="radio"/> 0-No		<input type="radio"/> 1-Yes <input type="radio"/> 0-No

"Serious problems" mean those that endangered the relationship.

A "problem" requires contact of some sort, either by telephone or in person.

Did anyone abuse you:	A. <u>Past 30 days</u>		B. <u>In your life</u>
F28. Physically (cause you physical harm)?	<input type="radio"/> 1-Yes <input type="radio"/> 0-No		<input type="radio"/> 1-Yes <input type="radio"/> 0-No
F29. Sexually (force sexual advances/acts)?	<input type="radio"/> 1-Yes <input type="radio"/> 0-No		<input type="radio"/> 1-Yes <input type="radio"/> 0-No

Comments:

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**FAMILY/SOCIAL RELATIONSHIPS**  
**(continued)**

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<b>Site:</b>	<b>Name Code:</b>	<b>ID Number:</b>	<b>Date of Assessment:</b> (mm/dd/yyyy)
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F30. How many days in the past 30 have you had serious conflicts with your family?

**For questions F32-34, please ask patient to use the Patient's Rating Scale**

F32. How troubled or bothered have you been in the past 30 days by these family problems? ☐ ☐ ☐ ☐ ☐

F34. How important to you *now* is treatment or counseling for these family problems? ☐ ☐ ☐ ☐ ☐

F31. How many days in the past 30 have you had serious conflicts with other people (excluding family)?

**For questions F33-35, ask the patient to use the patient's rating scale**

F33. How troubled or bothered have you been in the past 30 days by social problems? ☐ ☐ ☐ ☐ ☐

Patient is rating his/her need for counseling for family problems, not whether they would be willing to attend.

F35. How important to you *now* is treatment or counseling for these social problems? ☐ ☐ ☐ ☐ ☐

- Include patient's need to seek treatment for such social problems as loneliness, inability to socialize, and dissatisfaction with friends. Patient rating should refer to dissatisfaction, conflicts, or other serious problems.

**CONFIDENCE RATINGS**

Is the above information significantly distorted by:

F37. Patient's misrepresentation? ☐ 1-Yes ☐ 0-No

F38. Patient's inability to understand? ☐ 1-Yes ☐ 0-No

Comments:

Please  
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## PSYCHIATRIC STATUS

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SerialNumber:

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Site:	Name Code:	ID Number:	Date of Assessment:	(mm/dd/yyyy)
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> / <input type="text"/> / <input type="text"/>	<input type="text"/>

How many times have you been treated for any psychological or emotional problems?

- \* P1. In a hospital or inpatient setting?   \* P2. As an outpatient or private patient?
- P3. Do you receive a pension for a psychiatric disability? ☐ 1-Yes ☐ 0-No

Do not include substance abuse, employment, or family counseling.

Treatment episode=a series of more or less continuous visits or treatment days, not the number of visits or treatment days.

Enter diagnosis in comments if known.

Have you had a significant period of time, (that was not a direct result of drug/alcohol use), in which you have:

A. Past 30 days

B. In your life

- |   |  |  |
|---|--|--|
| P4. Experienced serious depression-sadness, hopelessness, loss of interest, difficulty with daily function? | <input type="radio"/> 1-Yes <input type="radio"/> 0-No | <input type="radio"/> 1-Yes <input type="radio"/> 0-No |
| P5. Experienced serious anxiety/tension-uptight, unreasonably worried, inability to feel relaxed?           | <input type="radio"/> 1-Yes <input type="radio"/> 0-No | <input type="radio"/> 1-Yes <input type="radio"/> 0-No |
| P6. Experienced hallucinations-saw things or heard voices that were not there?                              | <input type="radio"/> 1-Yes <input type="radio"/> 0-No | <input type="radio"/> 1-Yes <input type="radio"/> 0-No |
| P7. Experienced trouble understanding, concentrating, or remembering?                                       | <input type="radio"/> 1-Yes <input type="radio"/> 0-No | <input type="radio"/> 1-Yes <input type="radio"/> 0-No |
| <hr/>   |  |  |
| P8. Experienced trouble controlling violent behavior including episodes of rage, or violence?               | <input type="radio"/> 1-Yes <input type="radio"/> 0-No | <input type="radio"/> 1-Yes <input type="radio"/> 0-No |
| P9. Experienced serious thoughts of suicide?  | <input type="radio"/> 1-Yes <input type="radio"/> 0-No | <input type="radio"/> 1-Yes <input type="radio"/> 0-No |
| P10. Attempted suicide?   | <input type="radio"/> 1-Yes <input type="radio"/> 0-No | <input type="radio"/> 1-Yes <input type="radio"/> 0-No |
| P11. Been prescribed medication for any psychological/emotional problem?                                    | <input type="radio"/> 1-Yes <input type="radio"/> 0-No | <input type="radio"/> 1-Yes <input type="radio"/> 0-No |

For questions P8-10, patient could have been under the influence of alcohol/drugs.

Comments:

Please  
PRINT CLEARLY

1	2	3	4	5	6	7	8	9	0
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A	B	C	D	E	F	G	H	I	J	K	L	M
N	O	P	Q	R	S	T	U	V	W	X	Y	Z

**PSYCHIATRIC STATUS**  
(continued)

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SerialNumber:

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41616

<b>Site:</b>	<b>Name Code:</b>	<b>ID Number:</b>	<b>Date of Assessment:</b> (mm/dd/yyyy)																							
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Comments:

P12 How many days in the past 30 have you experienced these psychological or emotional problems?

--	--

- This refers to problems noted in question P4-10

For questions P13 & 14, please ask patient to use the Patient's Rating Scale

P13 How much have you been troubled or bothered by these psychological or emotional problems in the past 30 days? ③ ① ② ③ ④

- Patient should be rating the problem days from question P12

P14 How important to you *now* is treatment for these psychological or emotional problems? ③ ① ② ③ ④

**CONFIDENCE RATINGS**

Is the above information significantly distorted by:

P22 Patient's misrepresentation? ☐ 1-Yes ☐ 0-No

P23 Patient's inability to understand? ☐ 1-Yes ☐ 0-No

Please  
PRINT CLEARLY

1	2	3	4	5	6	7	8	9	0
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A	B	C	D	E	F	G	H	I	J	K	L	M
N	O	P	Q	R	S	T	U	V	W	X	Y	Z



# CODES

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SerialNumber:

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<b>Site:</b>	<b>Name Code:</b>	<b>ID Number:</b>	<b>Date of Assessment:</b> (mm/dd/yyyy)																		
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Patient Rating Scale	Comments (include question number)
0-Not at all 1-Slightly 2-Moderately 3-Considerably 4-Extremely	
<b>Hollingshead Categories</b>  1. Higher executive, major professional, owner of large business.  2. Business manager if medium sized business, lesser professionals, i.e., nurses, opticians, pharmacists, social workers, teachers.  3. Administrative personnel, manager, minor professionals, owner/Proprietor of small business, i.e., bakery, car dealership, engraving business, plumbing business, florist, decorator, actor, reporter, travel agent. 4. Clerical and sales, technicians, small businesses (bank teller, bookkeeper, clerk, draftsman, timekeeper, secretary).  5. Skilled manual-usually having had training (barber, brakeman, chef, electrician, fireman, machinist, mechanic, paperhanger, painter, repairman, tailor, welder, police, plumber).  6. Semi-skilled (hospital aide, painter, bartender, bus driver, cutter, cook, drill press, garage guard, checker, waiter, spot welder, machine operator).  7. Unskilled (attendant, janitor, construction helper, unspecified labor, porter, include unemployed).  8. Homemaker.  9. Student, disabled, no occupation.	

Please  
PRINT CLEARLY

1	2	3	4	5	6	7	8	9	0
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A	B	C	D	E	F	G	H	I	J	K	L	M
N	O	P	Q	R	S	T	U	V	W	X	Y	Z



## **Appendix 24      Beck Depression Inventory II (BDI-II)**

To be supplied by Indivior Inc.

<http://www.pearsonclinical.com/psychology/products/100000159/beck-depression-inventoryii-bdi-ii.html?Pid=015-8018-370&Mode=summary#tab-details>

## **Appendix 25      Brief Pain Inventory (BPI) Short Form**

To be supplied by Indivior Inc.

[http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/BPI\\_UserGuide.pdf](http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/BPI_UserGuide.pdf)

## **Appendix 26            Sponsor Signatures**

**Study Title:**            An Open-Label, Long-Term Safety and Tolerability Study of Depot Buprenorphine (RBP-6000) in Treatment-Seeking Subjects With Opioid Use Disorder

**Study Number:**        RB-US-13-0003

**Final Date:**            04 August 2016

This clinical study protocol was subject to critical review and has been approved by the Sponsor and contracted Medical Monitor.

Signed: \_\_\_\_\_ Date: \_\_\_\_\_  
[Redacted Signature]  
Sr. Vice President, Global Clinical Development  
Indivior Inc.

Signed: \_\_\_\_\_ Date: \_\_\_\_\_  
[Redacted Signature]  
Medical Monitor  
PRA Health Sciences.

## **Appendix 27**

## **Investigator's Signature**

**Study Title:** An Open-Label, Long-Term Safety and Tolerability Study of Depot Buprenorphine (RBP-6000) in Treatment-Seeking Subjects With Opioid Use Disorder

**Study Number:** RB-US-13-0003

**Final Date:** 04 August 2016

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed: \_\_\_\_\_

Date: \_\_\_\_\_

Printed Name and Credentials:

Title:

Site Name:

Address:

Telephone: