NCT02896296

Study Number: INDV-6000-301

Title: An Open-Label, Depot Buprenorphine (RBP-6000) Treatment Extension Study in Subjects With Opioid Use Disorder

Protocol Date: 30 September 2016

Clinical Study Protocol: INDV-6000-301

Study Title:	An Open-Label, Depot Buprenorphine (RBP-6000) Treatment Extension Study in Subjects with Opioid Use Disorder
Study Number:	INDV-6000-301
Study Phase:	3
Product Name:	RBP-6000
IND Number:	107,607
Indication:	Treatment of Opioid Use Disorder
Investigators:	Multicenter
Sponsor:	Indivior Inc. 10710 Midlothian Turnpike, Suite 430 Richmond, VA 23235

Sponsor Contact: [redacted]
Head Late Stage Development, Global Clinical Development

Medical Monitor: [redacted]
Scientific Research Fellow, Global Clinical Development

	Date
Original Protocol:	24 June 2016
Amendment 1	30 September 2016

SYNOPSIS

Sponsor:
Indivior Inc.

Name of Finished Product:
RBP-6000, 18% buprenorphine sterile solution for subcutaneous (SC) injection

Name of Active Ingredient:
Buprenorphine

Name of Inactive Ingredient:
ATRIGEL® Delivery System

Study Title:
An Open-Label, Depot Buprenorphine (RBP-6000) Treatment Extension Study in Subjects with Opioid Use Disorder

Study Number:
INDV-6000-301

Study Phase: Phase 3

Study Objective:
To provide ongoing treatment with RBP-6000 and safety monitoring for subjects who complete the RB-US-13-0003 study and for whom a new treatment venue has not been identified or arranged.

Study Design:
This is a multicenter, open-label, RBP-6000 treatment extension study in which approximately 300 subjects diagnosed with Opioid Use Disorder (OUD) will be enrolled. Enrollment is defined as the first dose of RBP-6000 administered for this study. Only subjects who have completed the End of Study (EOS) procedures for Study RB-US-13-0003, have signed the INDV-6000-301 informed consent form (ICF), and meet all the enrollment criteria may be considered for inclusion in this study.

The institutional review board (IRB) approved ICF may be shared with the potential subject up to 2 months before EOS Visit for Study RB-US-13-0003 in order to discuss this study as a possible treatment option. However, the ICF for Study INDV-6000-301 must not be signed until all assessments for the RB-US-13-0003 EOS Visit are complete.

The RB-US-13-0003 EOS assessments completed at the EOS Visit will serve as part of the screening assessments for this study. In addition, medical history will be collected, height measured, and subjects will be requested to complete a Columbia Suicide Severity Rating Scale (C-SSRS) baseline survey. The same-day Study RB-US-13-0003 EOS Visit / INDV-6000-301 Screening Visit will also be considered Day 1 of this study.

On Day 1, eligible subjects will receive a subcutaneous (SC) injection of RBP-6000. For each injection, subjects may receive either a dose of 100 mg RBP-6000 or 300 mg RBP-6000, based on the medical judgment of the Investigator. Following RBP-6000 injection, vital signs and the injection site will be assessed. The injection site will be assessed by the site for pain, tenderness, warmth, itching, erythema, inflammation or swelling, and bruising using a 5-point severity scale

(the Injection Site Grading Scale). In addition, the subject will assess their own injection site pain using a visual analog scale (VAS) (referred to as the Injection Site Pain VAS). Before departing the site, the subject will also be assessed for adverse events (AEs) and use of concomitant medications.

Subjects will not be permitted to receive supplemental buprenorphine during the RBP-6000 treatment period (Day 1 to EOS/ET Visit). Subjects who require supplemental buprenorphine pharmacotherapy during the RBP-6000 treatment period will be withdrawn from the study and referred for appropriate treatment.

Subjects will return to the site for monthly injection visits every 28 days (-2 / +7 days) for a total of up to 6 injections. Subjects are not required to complete all 6 injections and may choose to "early terminate" (ET) the study at any time.

At each subsequent visit (Injection Visits 2 through 6) the following procedures and assessments will be performed: urine pregnancy test for all female subjects who are of childbearing potential before each injection; evaluation of previous injection site for potential reaction and evidence of attempts to remove the depot; collection of vital signs pre- and post-injection; RBP-6000 injection, urine drug screen (UDS); C-SSRS since last visit, counseling (manual-guided behavioral therapy); local injection site grading; subject self-assessment of injection site pain (Injection Site Pain VAS); use of concomitant medications; and assessment for AEs. Laboratory tests (hematology, chemistry and urinalysis) may be requested by the Investigator on an ad-hoc basis as necessary to further examine any AEs.

Alternative treatment options should be assessed at least two months before EOS at each visit, however it is recommended where possible to assess at every visit.

At the EOS/ET Visit, the following procedures and assessments will be performed: urine pregnancy test for all female subjects who are of childbearing potential; evaluation of previous injection site for potential reaction and evidence of attempts to remove the depot; vital sign measurements; UDS; C-SSRS since last visit, counseling (manual-guided behavioral therapy); use of concomitant medications; assessment for AEs; brief physical exam; height and body weight measurement (to determine a subject's body mass index [BMI]); hip and waist circumference measurement (to determine a subject's hip-to-waist ratio); and laboratory tests (hematology, chemistry, urinalysis).

Approximately 4 weeks after EOS/ET Visit, all subjects should be contacted by telephone for a safety follow-up assessment of AEs and use of any concomitant medications.

Study Population:

All subjects who completed the RB-US-13-0003 study may be eligible to enroll into this study. Approximately 300 subjects will be enrolled.

Test Product, Dose, and Mode of Administration:

300 mg buprenorphine in RBP-6000, subcutaneous injection

100 mg buprenorphine in RBP-6000, subcutaneous injection

Duration of Study Treatment:

This will be a multiple-dose study, with the first investigational product administration (RBP-6000) occurring on Study Day 1. The expected duration of participation for each subject is up to approximately 29 weeks, consisting of a 25-week, open-label treatment period and a safety

follow-up phone call at 4 weeks after the EOS/ET Visit.

Safety Assessments:
Safety will be assessed throughout the entire study on the basis of the following: AEs, serious adverse events (SAE)s, discontinuations from study due to AEs; local injection site tolerability (based on injection site grading); injection site pain using a subject-reported VAS; suicidality using the C-SSRS, use of concomitant medications; clinically significant changes in clinical laboratory results; vital sign measurements; physical examination findings; and measurements of body weight, height, waist and hip circumference (for calculation of BMI and abdominal fat measurement [waist-to-hip ratio]).

Statistical Methods:

A Statistical Analysis Plan (SAP) will be finalized 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 subjects who completed Study RB-US-13-0003 will be enrolled into 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 C-SSRS, concomitant medications; changes in clinical laboratory results (hematology, chemistry and urinalysis); vital sign measurements; physical examination results; body weight, height, BMI, and abdominal fat measurement (waist-to-hip ratio). Safety variables will be described using descriptive statistics for continuous endpoints (e.g., mean, median, standard deviation (SD), minimum and maximum) and frequency counts with percentages for discrete endpoints.

Baseline is defined as the value collected at Screening. No imputation of missing values will be performed.

Date of Original Protocol: 24 June 2016

Date of Protocol Amendment 1: 30 September 2016

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate transaminase
BMI	Body mass index
BUN	Blood urea nitrogen
CRA	Clinical Research Associate
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
eCRF	Electronic case report form
ECG	Electrocardiogram
EOS	End of study
ET	Early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDL	High-density lipoprotein
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IM	Intramuscular
IMP	Investigational medicinal product
IRB	Institutional review board
IV	Intravenous
IWRS	Interactive web response system
LDL	Low-density lipoprotein
NMP	N-methyl-2-pyrrolidone
OTC	Over-the-counter
OUD	Opioid Use Disorder

PK	Pharmacokinetic
PLGH	Poly (DL-lactide-co-glycolide)
QA	Quality Assurance
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SL	Sublingual
SOE	Schedule of events
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
UDS	Urine Drug Screen
US/USA	United States/United States of America
VAS	Visual analog scale
WHO	World Health Organization

1 INTRODUCTION

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 (OUD) 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). These high costs have prompted researchers to seek new medications and treatment strategies for opioid dependence aiming to reduce the use of prescription or illicit opioids.

Buprenorphine, a mu-opioid receptor partial agonist and kappa-opioid receptor antagonist, is one such medication that has had a significant role in expanding access to effective opioid dependence treatment. Buprenorphine has been approved for use in the treatment of opioid dependence in a number of countries worldwide. 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.

The sponsor is currently developing a buprenorphine depot (RBP-6000), which is a subcutaneously injected for the treatment of OUD. It contains buprenorphine in the ATRIGEL Delivery System and provides sustained plasma levels of buprenorphine over a minimum of 28 days (RBP-6000 IB).

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-2-pyrrolidone (NMP). The ATRIGEL Delivery System is well characterized. It is currently used in 7 approved products worldwide, including 4 ELIGARD® products (subcutaneous [SC] depot formulations of leuprolide acetate), ATRIDOX® (doxycycline hyclate applied to the periodontal pocket), the ATRISORB® Bioabsorbable Guided Tissue Regeneration Barrier for periodontal application, and the ATRISORB-D Barrier (ATRISORB with doxycycline) for periodontal guided tissue regeneration.

1.1 Background Information

To date, there have been 4 clinical studies completed using RBP-6000 (Table 1).

Table 1 Summary of Completed RBP-6000 Clinical Studies

Study	Study Title	IMP (Dose)	Most Common AE(s) Possibly Related to Study Drug	Other Safety
RB-US-10-0011	A Single-Dose, Open-Label Study of Depot Buprenorphine (RBP-6000) in Opioid Dependent Individuals	RBP-6000 (20 mg)	Drug withdrawal syndrome Injection site pain Rebound hypertension Constipation Headache Injection site warmth Respiratory rate increased	No clinically significant trends in vital signs, ECGs, clinical laboratory tests, or physical examinations. No deaths or SAEs related to treatment and no subjects discontinued due to an AE.
RB-US-11-0020	A Multicenter, Open-Label, Single Ascending-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Depot Buprenorphine (RBP-6000) in Opioid-Dependent Subjects	RBP-6000 (50 mg, 100 mg, and 200 mg)	Drug withdrawal syndrome Constipation Diarrhea Nausea Injection site pain	No clinically significant trends in vital signs, ECGs, clinical laboratory tests, or physical examinations. No deaths or SAEs related to treatment and no subjects discontinued due to an AE.
RB-US-12-0005	An Open-Label, Multicenter, Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics, Efficacy Markers, and Opioid Receptor Availability of Subcutaneous Injections of Depot Buprenorphine (RBP-6000) in Treatment Seeking Opioid Dependent Subjects	RBP-6000 (50 mg, 100 mg, 200 mg, and 300 mg)	Drug withdrawal syndrome Vomiting Constipation Musculoskeletal pain Anxiety Upper Respiratory Tract Infection Liver function test abnormal	No clinically significant trends in hematology, serum chemistry, urinalysis, vital signs, or ECGs. There were 9 SAEs during the study; 3 subjects withdrawn due to SAEs; 8 subjects withdrawn from the study due to a TEAE. None of the above events were considered related to study medication.
RB-US-13-0002	A Multiple-Dose Study of Blockade of Subjective Opioid Effects, Pharmacokinetics, and Safety of Subcutaneous Injections of Depot Buprenorphine (RBP-6000) in Subjects with Opioid Use Disorder	RBP-6000 (300 mg)	Drug withdrawal syndrome Headache Anxiety Constipation Liver function test abnormal Injection site reaction	No clinically significant trends in hematology, serum chemistry, urinalysis, vital signs, and ECGs. No deaths, no SAEs, and no withdrawals from the study due to a TEAE.

AE = Adverse Event; ECG = Electrocardiogram; IMP = Investigational medicinal product; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event.

In summary, doses of 50, 100, 200 and 300 mg RBP-6000 have been administered to male and female subjects and have been safe and well tolerated. (RBP-6000 IB).

A population pharmacokinetic (PK) model was developed to characterize the disposition of buprenorphine and norbuprenorphine following SC injection of RBP-6000 (Nasser 2014). 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). The model simulations indicated that the desired 70% mu opioid receptor occupancy may be achieved after multiple doses of 200 mg of RBP-6000. The 300 mg dose was considered to be a full opioid blockade dose.

There are currently 2 studies in the process of being completed and 1 study is ongoing:

- **RB-US-13-0006** – A Single-Center, Randomized, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Depot Buprenorphine (RBP-6000) Using Poly (DL-lactide-co-glycolide) Polymer of Two Different Molecular Weights (Low and High Molecular Weights as Test Treatments) in Comparison to Intermediate Molecular Weight (Reference Treatment) in Treatment-Seeking Subjects with Opioid Use Disorder. [Study Status: Study has concluded/analysis in progress]

    - An investigational Phase I PK study evaluating the PK, safety, and tolerability of 300 mg RBP-6000 using different molecular weights of the PLGH within the ATRIGEL delivery system, in Treatment-Seeking Subjects with OUD.

- **RB-US-13-0001** - A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study To Assess the Efficacy, Safety, and Tolerability of Multiple Subcutaneous Injections of Depot Buprenorphine (RBP-6000 [100 mg and 300 mg]) Over 24 Weeks in Treatment-Seeking Subjects with Opioid Use Disorder. [Study Status: Study has concluded/analysis in progress]

    - A Phase III double-blind, placebo controlled efficacy study. The study is assessing the Efficacy, Safety, and Tolerability of 6 Subcutaneous Injections of RBP-6000 [100 mg and 300 mg] (or placebo) in approximately 500 treatment-seeking subjects with OUD. Subjects who successfully completed this study were permitted to enroll in study RB-US-13-0003, if eligible.

- **RB-US-13-0003** - An Open-Label, Long-Term Safety and Tolerability Study of Depot Buprenorphine (RBP-6000) in Treatment-Seeking Subjects With Opioid Use Disorder. [Study Status: Ongoing/analysis is pending]

    - A Phase III, open-label, long-term safety and tolerability Study of RBP-6000 in approximately 600 treatment-seeking subjects with OUD. Subjects in this study will be dosed with a maximum of 12 injections of RBP-6000 (if enrolled directly

onto this study), and a maximum of 6 injections if enrolled from study RB-US-13-0001.

1.2 Rationale for Dose Selection

The doses proposed in this study are 100 mg RBP-6000 and 300 mg RBP-6000, which are the doses subjects are currently receiving in the RB-US-13-0003 study. These doses were chosen in the RB-US-13-0001 and RB-US-13-0003 studies as modeling and simulation (Nasser 2014) demonstrated that the 300 mg SC dose is an appropriate dose to assess for efficacy. The 100 mg RBP-6000 dose is provided because it is recognized that some individuals may need or desire lower dosages.

Doses of RBP-6000 may be adjusted up or down (to either 100 mg or 300 mg) throughout the course of the study based on the medical judgment of the Investigator.

1.3 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., sublingual [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 purpose of this study (INDV-6000-301) is to continue to provide up to an additional 6 injections of RBP-6000 for those subjects who have **completed** study RB-US-13-0003 and where a new treatment venue has not yet been identified, or arranged while ensuring their use of the product is monitored for safety.

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.

1.4 Good Clinical Practice

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor, designees and Investigator abide by Good Clinical Practice (GCP) as described in 21CFR parts 50, 54, 56, and 312 as well as in the

International Council for Harmonisation (ICH) Guidelines Topic E6 (R1): Guideline for Good Clinical Practice". The study will also be carried out in accordance with local legal and regulatory requirements.

2 STUDY OBJECTIVE

To provide ongoing treatment with RBP-6000 and safety monitoring for subjects who complete the RB-US-13-0003 study and for whom a new treatment venue has not been identified or arranged.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multicenter, open-label, RBP-6000 treatment extension study in which approximately 300 subjects diagnosed with Opioid Use Disorder (OUD) will be enrolled. Enrollment is defined as the first dose of RBP-6000 administered for this study. Only subjects who have completed the End of Study (EOS) procedures for Study RB-US-13-0003, have signed the INDV-6000-301 informed consent form (ICF), and meet all the enrollment criteria may be considered for inclusion in this study.

The IRB approved ICF may be shared with the potential subject up to 2 months before EOS Visit for Study RB-US-13-0003 in order to discuss this study as a possible treatment option. However, the ICF for Study INDV-6000-301 must not be signed until all assessments for the RB-US-13-0003 EOS Visit are complete.

The RB-US-13-0003 EOS assessments completed at the EOS Visit will serve as part of the screening assessments for this study. In addition, medical history will be collected, height measured, and the subjects will be requested to complete a Columbia Suicide Severity Rating Scale (C-SSRS) baseline/screening survey. The same-day Study RB-US-13-0003 EOS Visit / INDV-6000-301 Screening Visit will also be considered Day 1 of this study.

On Day 1, eligible subjects will receive a subcutaneous (SC) injection of RBP-6000. For each injection, subjects may receive either a dose of 100 mg RBP-6000 or 300 mg RBP-6000, based on the medical judgment of the Investigator. Following RBP-6000 injection, vital signs and the injection site will be assessed. The injection site will be assessed for pain, tenderness, warmth, itching, erythema, inflammation or swelling, and bruising using a 5-point severity scale (Injection Site Grading Scale). In addition, the subject will assess their own injection site pain using a visual analog scale (VAS) (referred to as the Injection Site Pain VAS). Before departing the site, the subject will also be assessed for adverse events (AEs) and use of concomitant medications.

Subjects will not be permitted to receive supplemental buprenorphine during the RBP-6000 treatment period (Day 1 to EOS/ET Visit). Subjects who require supplemental buprenorphine pharmacotherapy during the RBP-6000 treatment period will be withdrawn from the study and referred for appropriate treatment. [Note: If subjects complete their EOS/ET Visit and a new treatment venue for them has not been identified, the Investigator may provide the subject further buprenorphine treatment or another appropriate treatment according to their own medical judgement.]

Subjects will return to the site for monthly injection visits every 28 days (-2 / +7 days) for a total of up to 6 injections. Subjects are not required to complete all 6 injections and may choose to "early terminate" (ET) the study at any time.

At each subsequent visit (Injection Visits 2 through 6) the following procedures and assessments will be performed: urine pregnancy test for all female subjects who are of childbearing potential before each injection; evaluation of previous injection site for potential reaction and evidence of attempts to remove the depot; collection of vital signs pre- and post-injection; RBP-6000 injection; urine drug screen (UDS); C-SSRS since last visit assessment, counseling (manual-

guided behavioral therapy); local injection site grading; subject self-assessment of injection site pain (Injection site Pain VAS); use of concomitant medications; and assessment for AEs.

Laboratory tests (hematology, chemistry and urinalysis) may be requested by the Investigator on an ad-hoc basis as necessary to further examine any AEs.

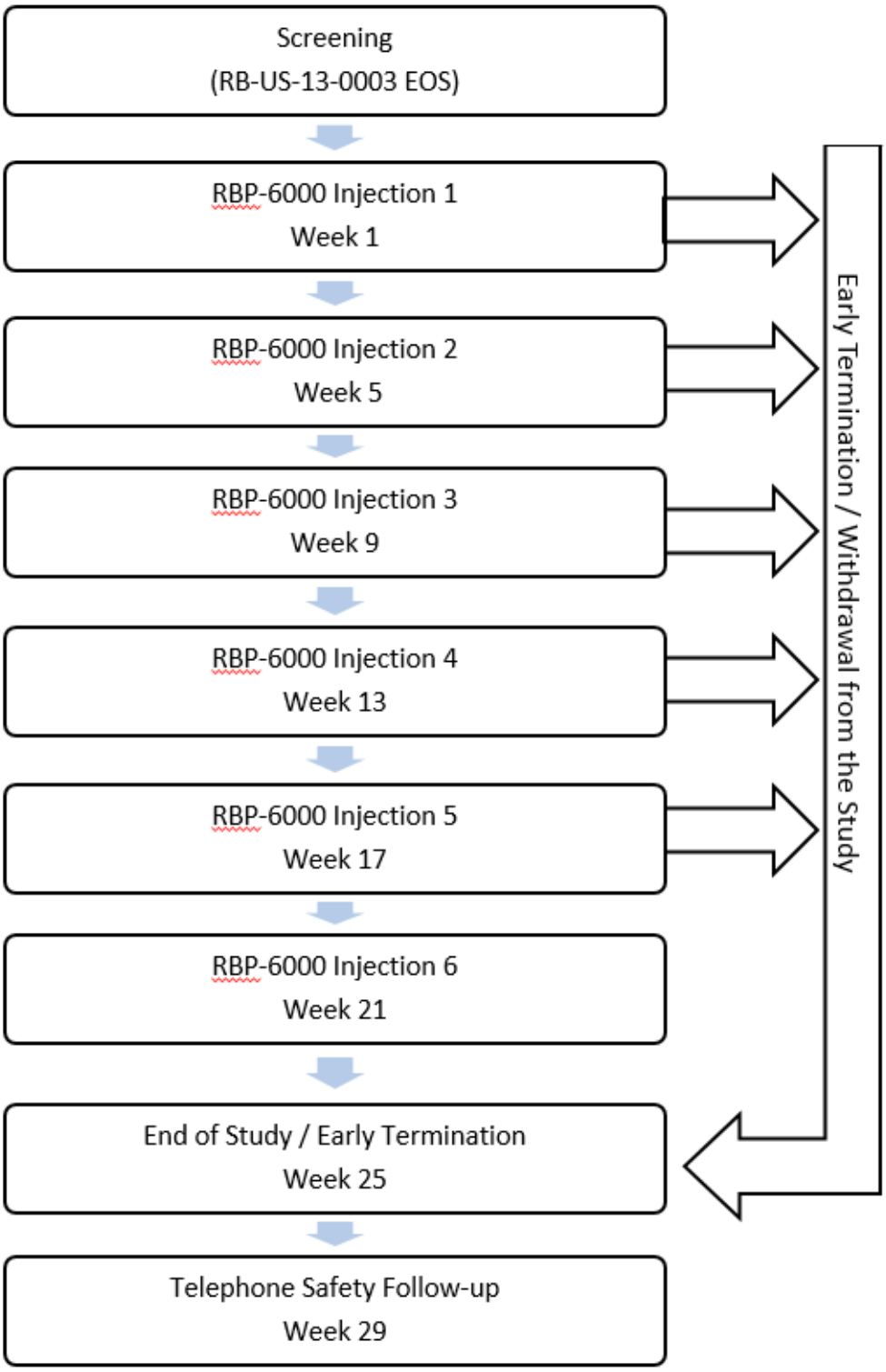
Alternative treatment options should be assessed at least two months before EOS at each visit, however it is recommended where possible to assess at every visit.

At the EOS/ET Visit, the following procedures and assessments will be performed: urine pregnancy test for all female subjects who are of childbearing potential; evaluation of previous injection site for potential reaction and evidence of attempts to remove the depot; vital sign measurements; UDS; C-SSRS "since last visit" assessment, counseling (manual-guided behavioral therapy); use of concomitant medications; assessment for AEs; brief physical exam; height and body weight measurement (to determine a subject's BMI); hip and waist circumference (to determine a subject's hip-to-waist ratio); and laboratory tests (hematology, chemistry, urinalysis).

Approximately 4 weeks after EOS/ET Visit, all subjects should be contacted by telephone for a safety follow-up assessment of AEs and use of any concomitant medications.

A schematic depicting the study design is presented in Figure 1. A complete list of procedures and assessments for subjects is in the Schedule of Events (SOE) in Appendix 1.

Figure 1 Study Overview



Note: RB-US-13-0003 EOS / Screening and RBP-6000 Injection 1 / Week 1 occurs on the same day (Day 1).

3.2 Rationale for Study Design

The purpose of this study is to provide up to an additional 6 injections of RBP-6000 for those subjects who have **completed** the RB-US-13-0003 study and for whom a new treatment venue has not yet been identified or arranged while ensuring their use of the product is monitored for safety. The study design includes only monthly visits with additional safety assessments while the long term safety and tolerability of RBP-6000 are being studied.

3.3 Study Duration and Dates

This will be a multiple-dose study, with the first IMP administration (RBP-6000) on Day 1. The expected maximum duration of participation for subjects is up to approximately 29 weeks consisting of a maximum 25-week open-label treatment period, and a safety follow-up phone call at 4 weeks after the EOS/ET Visit.

Subjects who receive at least 1 dose of RBP-6000 and discontinue the trial for any reason will be required to complete the EOS/ET Visit and the safety follow-up telephone call.

4 STUDY POPULATION SELECTION

4.1 Study Population

Approximately 300 subjects will be enrolled into this study. The study population will consist of individuals diagnosed with OUD who are seeking treatment for opioid use disorder, and who have completed the EOS for RB-US-13-0003 study.

4.2 Inclusion Criteria

Subjects who have successfully completed Study RB-US-13-0003 EOS 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. Completed the End of Study Visit for the RB-US-13-0003 study.
3. Be considered eligible in the medical judgment of the Investigator.
4. Females: Women of childbearing potential (defined as all women who are not surgically sterile or postmenopausal for at least 1 year prior to ICF) 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 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 (for a period of at least 1 month) 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.
5. Subjects must agree not to take any buprenorphine products other than those administered during the current study throughout participation in the study.
6. Subjects must be willing to adhere to study procedures.

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Subject compliance issues during participation in the RB-US-13-0003 study which, in the opinion of the Investigator, could potentially compromise subject safety.
2. Women of childbearing potential who have a positive pregnancy test at the RB-US-13-0003 EOS Visit, who are pregnant or breastfeeding, seeking pregnancy, or failing to use adequate contraceptive methods during the study.
3. History of suicidal ideation within 28 days prior to signing the ICF as evidenced by answering “yes’ to questions 4 or 5 on the suicidal ideation portion of the C-SSRS “since

last visit" assessment (completed in the EOS Visit for Study RB-US-13-0003); or history of a suicide attempt (per the C-SSRS "screening/baseline" assessment for the current study) in the 6 months prior to signing the ICF.

4. Taking any cytochrome P450 3A4 and 2C8 inducers and inhibitors; self-reported additional buprenorphine (in addition to amount administered per protocol as part of subject's participation in Study RB-US-13-0003); or OTC and/or herbal supplements with the potential to prolong QTc as per Section 6.10.1 within 28 days of Day 1; unless prior written approval is obtained from the Medical Monitor.

5 STUDY TREATMENTS

5.1 Description of Treatment

RBP-6000 contains buprenorphine in the ATRIGEL delivery system. RBP-6000 is manufactured according to Good Manufacturing Practice standards. 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 2: IMP Preparation and Dispensing Procedures for detailed dosage instructions).

5.2 Treatments Administered

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 2.

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 35 days** (28 days -2/+7 days) and will be given on alternate sides of the subject's abdomen (see Appendix 2 and the Pharmacy Manual for detailed information on administration).

If at an Injection Visit there is a safety concern with administration of RBP-6000, dosing can be delayed within the specified window. No injections are permitted outside of this window without prior consent from the Medical Monitor.

Time of dose is defined as the time the RBP-6000 SC injection is complete.

5.4 Method of Assigning Subjects to Treatment Groups

There are no distinct treatment groups in this study. Doses of either 100 mg or 300 mg RBP-6000 may be administered to the subject, based on the medical judgment of the Investigator. The reason for dose change should be captured in the electronic case report form (eCRF)

Subjects will retain the subject number assigned to them in the RB-US-13-0003 study. The subject number will be recorded in the source document and eCRF.

5.5 Blinding

Not applicable; this is an open-label study

5.6 Restrictions

Subjects should be advised to avoid strenuous exercise.

See section 6.10.1 for prohibited concomitant medications.

5.7 Dosing Compliance

IMP will be administered by a designated and qualified licensed healthcare provider, unless a designated person is pre-approved by the Sponsor. The time of dose and any dosing observations will be recorded in source documentation; in addition, time of dose will be recorded in the eCRF. Time of dose is defined as the time the RBP-6000 SC injection is complete. The Investigator or designated individual will maintain a log of all IMPs dispensed and returned (if applicable). The Investigator agrees not to supply RBP-6000 to any person except study personnel for SC injection of subjects in this study.

5.8 Packaging and Labeling

RBP-6000 will be identified as an investigational compound and will be packaged and labeled in a manner consistent with the study design and applicable regulations.

5.9 Product Quality Complaints

Any issues noted (something out of the ordinary) with the packaging, labeling or RBP-6000 product should be immediately reported. Please refer to the Pharmacy Manual for detailed instructions.

5.10 Storage and Accountability

RBP-6000 should be stored under refrigerated conditions at 2ºC to 8ºC (36°F to 46°F). Temperature excursions in the range of 8°C to 25°C (46°F to 77°F) are permitted for a maximum duration of 48 hours; temperature excursions in the range of -20°C to 2°C (-4°F to 36°F) are permitted for a maximum duration of 7 days. Temperature excursions outside of this range should be reported to the Sponsor immediately and approval should be obtained before use, please refer to the pharmacy manual for details.

The Investigator or designee is responsible for ensuring that all IMP received at the site is inventoried and accounted for throughout the study. IMP 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 Investigator must ensure that proper conditions exist for storage of study treatments. The dispensing of IMP to the subject must be documented. Re-supply of RBP-6000 will be managed by IWRS and automatic shipments will

be processed based upon enrollment status and current available stock at the site (see Pharmacy Manual for further information on re-supply shipments).

Unused IMP must be available for verification by the site's CRA during on-site monitoring visits. All used syringes components will be disposed of in accordance with the site's standard operating procedure (SOP) or pharmacy destruction policy, which will be reviewed by the CRA before use. All used IMP packaging components should be retained for the verification by the CRA before disposal is permitted.

5.11 IMP Retention at Study Site

All unused RBP-6000 must be returned to the warehouse before the end of the study. The warehouse will arrange for the appropriate and timely destruction of all returned, unused RBP-6000.

6 STUDY PROCEDURES

The SOE for this study is provided in Appendix 1.

6.1 Medical History

A detailed medical history will be re-collected for this study up until signing the ICF. This will include information regarding the subject's full history of medical and psychiatric conditions; diagnoses; procedures; concomitant medications; demographic information; use of tobacco, drugs of abuse, alcohol, and caffeine; and any other noteworthy medical information, including suicidality measured using the C-SSRS, hospitalizations and the reason for admission (medical/surgical/psychiatric/other). Any pre-planned surgeries or procedures outside of the scope of this study should also be considered as part of medical history. The medical history also should include medical events that occurred during a subject's participation in Study RB-US-13-0001 and/or RB-US-13-0003, and are deemed relevant in the opinion of the Principal Investigator. Any relevant updates to medical history information that the Investigator or medically-qualified designee becomes aware of during the course of the study should also be recorded.

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.

6.2 Physical Examination

A physical examination will be performed by the Investigator or medically qualified designee at the EOS Visit for study RB-US-13-0003. Assessments for general appearance, chest/lungs, heart, abdomen and the brief neurological assessment will serve as the screening values for the present study. If any clinically significant abnormal findings were observed before the INDV-6000-301 ICF was signed (including those noted during the RB-US-13-0003 EOS), these findings should be recorded on the Medical History case report form (eCRF).

A brief physical exam will be repeated at EOS for INDV-6000-301. The physical examination will consist of an examination of the following: general appearance, chest/lungs, heart, abdomen and a brief neurological assessment. The examination will not include a pelvic, breast, or rectal examination. If any clinically significant change from screening is noted, it will be reported as an AE and followed up to resolution or until reaching a stable end point.

6.3 Body Mass Index and Hip-to-Waist Ratio

A subject's weight (kg) (in ordinary indoor clothing with shoes off) will be measured at the EOS Visit for Study RB-US-13-0003. A subject's height (cm) will be re-measured at the INDV-6000-301 Screening Visit. These measurements (weight and height) will be inputted into the eCRF in order to calculate a BMI (i.e., BMI calculation will be done automatically in the electronic data capture system). BMI is defined as the subject's weight in kg divided by the square of the subject's height in meters (kg/m^2). (Note: Calculation of BMI in the EOS Visit for Study RB-

US-13-0003 will use the height measurement originally taken at screening for the prior study.) A subject's amount of abdominal fat (waist-to-hip ratio) will be determined using measurement of both waist and hip circumference (cm) at the EOS Visit for Study RB-US-13-0003; this previously calculated waist-to-hip ratio will be recorded in the eCRF. These values will serve as the screening values for this study. The above assessments will be repeated at the EOS/ET Visit for INDV-6000-301, as detailed in the SOE (Appendix 1).

6.4 Vital Signs

Evaluation of vital signs will be performed after the subject has been supine for ≥ 3 minutes and will include a measurement of systolic and diastolic blood pressure, 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).

6.5 Clinical Laboratory Tests

6.5.1 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 Accreditation (or Certificate of Waiver for CLIA-waived tests) issued by the Center for Medicare & Medicaid Services. The laboratory assessments will include routine and screening laboratory tests.

See the SOE in Appendix 1 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. 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

Hematology:	Serum Chemistry:
Hematocrit	Albumin
Hemoglobin	Alkaline phosphatase (ALP)
Mean corpuscular hemoglobin	Alanine aminotransferase (ALT)
Mean corpuscular hemoglobin concentration	Amylase
Mean corpuscular volume	Aspartate aminotransferase (AST)
Platelet count	Blood urea nitrogen
Red blood cell count	Calcium
White blood cell count with differential	Calculated creatinine clearance[c]
	Carbon dioxide
Urinalysis:	Chloride
Appearance	Creatinine
Bilirubin	Creatine kinase and subtypes
Color	Gamma-glutamyl transferase
Glucose	Globulin
Ketones	Glucose (non-fasting)
Leucocyte esterase	High-density lipoprotein (HDL)
Microscopic examination of sediment[a]	Lactate dehydrogenase
Nitrite	Lipase
Occult blood	Low-density lipoprotein (LDL)
pH	Magnesium
Protein	Phosphorus
Specific gravity	Potassium
Urobilinogen	Sodium
	Total bilirubin
Pregnancy:	Direct bilirubin
Urine Pregnancy (only for females not postmenopausal or surgically sterile for at least 1 year)	Total cholesterol
	Total protein
	Triglycerides
Urine Drug Screen:	Uric acid
Opioids[b]	
Cocaine	
Amphetamines	
Methadone	
Cannabinoids	
Barbiturates	
Benzodiazepines	
Methamphetamine	
Phencyclidine	

[a] 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).

[b] Oxycodone may not show up in all opiate assays and should be assessed separately.

[c] Creatinine clearance will be calculated according to the Cockcroft-Gault equation.

6.5.2 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.

6.5.3 Reference Ranges

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

6.5.4 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.

Any liver abnormality > 3 x ULN should be carefully assessed by the Investigator to determine whether it should be considered an AE. Guidance for the procedures to follow for elevated liver function tests are provided in Appendix 8.

6.6 Suicidality Assessments

The C-SSRS is a questionnaire designed for assessment of suicidal ideation and behavior in adolescents and adults (Posner 2011). Suicidality assessment will be conducted according to the SOE table in Appendix 1, using two versions of the C-SSRS ("baseline/screening" and "since last visit"). The C-SSRS "baseline/screening" assessment will include both a lifetime and past 6-month time interval. The two C-SSRS versions are presented in Appendix 4 and Appendix 5.

If a subject becomes suicidal during the study, the Investigator should provide 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 6.12.1).

If there is a positive ("yes") response on the C-SSRS ("since last visit") assessment 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.

6.7 Local Injection Site Tolerability

6.7.1 Injection Site Evaluation

At Injection Visits 2 through the EOS/ET Visit, the local injection site will be evaluated for potential reaction and evidence of any attempts to remove the depot medication following a previous injection of RBP-6000. This evaluation should be performed by the Investigator or a trained and qualified licensed healthcare professional. Any detected removal attempts should be

discussed with the Medical Monitor to determine whether the subject should be terminated from the study. In addition, detection of any depot removal attempt at the EOS Visit for the prior study (Study RB-US-13-0003) should be discussed with the Medical Monitor to determine whether a subject should be enrolled into the current study.

Depot removal attempts are to be captured in the e-CRF (using "Yes" or "No" answers).

6.7.2 Injection Site Grading

Local injection site grading will be performed by the Investigator or a trained and qualified licensed healthcare professional, unless a designated person is pre-approved by the Sponsor, according to the SOE in Appendix 1. Grading should be performed 1 hour (± 30 minutes) post-completion of injection. 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 5-point Injection Site Grading Scale in Appendix 6.

6.7.3 Injection Site Pain Visual Analog Scale (VAS)

Injection site pain will be assessed by the subject at each Injection Visit with a 100 mm VAS scale ranging from 0 to 100, where 0 represents "no pain" and 100 represents "maximum pain" (Appendix 7). The injection site pain VAS scores will be obtained approximately 1 hour after each injection. The timing of the injection site pain VAS assessment should be measured starting from the end of the injection. In addition to self-rating pain level 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?

Copies of any pre-printed VAS paper forms to be used by subjects for self-assessment of their injection site pain must be checked to confirm that the VAS rating scale measures exactly 100 mm (3.94 in) in length.

6.8 Pharmacokinetic Assessments

Not Applicable

6.9 Adverse Events Assessments

6.9.1 Adverse Event Definition

In accordance with ICH and United States Food and Drug Administration (FDA) guidance, any untoward medical occurrence incurred by a subject that occurs after the first study-related procedure to the completion of the Safety Follow-Up Visit 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 of the RB-US-13-0003 EOS visit will be recorded in the eCRF for this study.

All subjects participating in the study that have a EOS/ET Visit will be contacted by telephone for a safety follow-up assessment of AEs (new or ongoing) and use of any concomitant medications.

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.

6.9.2 Treatment-Emergent Adverse Event Definition

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

6.9.3 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 site 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. Any ongoing AEs reported in the RB-US-13-0003 study will be recorded in the eCRF for this study.

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.

6.9.4 Timing

AEs will be captured from the time the subject gives informed consent until the subject completes the Safety Follow-Up Visit.

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 (see Section 6.1).

6.9.5 Severity

Adverse events with changes in severity should be documented as separate events.

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.

6.9.6 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 IMP.

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

Not Related: Data are available to identify a clear alternative cause for the AE other than the IMP.

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).

6.9.7 Expectedness

An unexpected AE is any AE, the nature and severity of which is not consistent with the IB for the IMP.

6.9.8 Clinical Significance

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

6.9.9 Clinical Laboratory Adverse Events

Changes in laboratory values or vital signs, or other safety parameters (e.g., 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.

It is noted that any liver abnormality > 3 x ULN should be carefully assessed by the Investigator to determine whether it should be considered an AE. Guidance for the procedures to follow for elevated liver function tests are provided in Appendix 8.

6.9.10 Serious Adverse Events

6.9.11 Serious Adverse Event 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.”

6.9.11.1 Suspected Unexpected Serious Adverse Event Definition

A suspected unexpected serious adverse reaction (SUSAR) is any SAE that, in its nature or severity, is inconsistent with available medication information (e.g., IB or Package Insert). Indivior Pharmacovigilance will determine if an SAE is a SUSAR.

6.9.11.2 Reporting Serious Adverse Events

All SAEs will 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 Medical Monitor.

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

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

In the event that medical discussion is required for an SAE, the Medical Monitor should be contacted:

[redacted]
24-hour number: [redacted]
Email: [redacted]

In the event of an emergency, a back-up has also been identified:

[redacted]
Email: [redacted]

The Investigator or designee must inform the institutional review board (IRB) immediately regarding any AE (does not have to be causally related) that is both serious and unexpected (SUSAR); 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 IB.

Subjects with ongoing SAEs at the Safety Follow-Up Visit that in the opinion of the Investigator or medically qualified Sub-investigator are associated with the study, will be followed and reported as described in Section 6.9.11.2.

6.9.12 Pregnancy

If a pregnancy is confirmed at any time during the study through a urine pregnancy test 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 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.

6.10 Concomitant Medication Assessments

The Investigator or designee will record any concomitant therapies given 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.

Concomitant therapies are defined as prescribed medications and over the counter (OTC) preparations, including herbal preparations and vitamins, other than study medication and supplementary medication that the subject receives within 28 days of screening and for the during the course of the study. 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.

Subjects who are medically prescribed benzodiazepines will be evaluated on a case-by-case basis for inclusion in the INDV-6000-301 study. The Investigator will discuss these subjects with the Medical Monitor before enrolling into the INDV-6000-301 study.

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

6.10.1 Prohibited Concomitant Medications

The sponsor must approve any prohibited concomitant medications before administration except in cases of immediate medical need. In cases of immediate medical need, consult the Medical Monitor as soon as possible following administration of a prohibited medication for any further questions and to ensure appropriate documentation. All concomitant medications should be recorded in the eCRF.

The following medications are prohibited:

- All cytochrome P450 3A4 and 2C8 inducers and inhibitors inclusive of, but not limited to those in Appendix 3
- Buprenorphine (in addition to RBP-6000 treatment)
- OTC and/or herbal supplements with the potential to prolong QTc. (For example: famotidine (e.g., Pepcid brand), ephedrine, and some Chinese herbal supplements.)

The use of all opioids should be avoided in this study.

- If the subject self-medicates with these medications, document reason for use appropriately.
- Any prescribed opioids for other uses (such as pain) should be discussed with the Medical Monitor.

The use of the following medications requires careful consideration, and should be discussed with the Medical Monitor. If treatment is necessary, careful monitoring is required for:

- prescription medications known to prolong the QTc interval
- general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, and sedative/hypnotics.

6.11 Counseling/Behavioral Therapy

After enrollment, subjects will receive manual-guided, individual behavioral therapy according to the SOE indicated in Appendix 1 . Behavioral therapy can be conducted by any appropriately trained staff member at the site. A reference manual will be provided to each site by the Sponsor.

6.12 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 comprises or may compromise data integrity, protocol compliance, or subject safety;
- AE that compromises or may compromise subject safety;
- Sponsor or Investigator terminates the study;
- Subject requests to be discontinued from the study (i.e., subject declines further study participation); or
- Subject becomes pregnant.

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.

6.12.1 Early Removal of RBP-6000

In the event of an emergency, toxicity is suspected, 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 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 ET assessments performed at the time of early removal of RBP-6000 and a safety follow up call 28 days later, as per the SOE (Appendix 1).

The extracted RBP-6000 depot will be disposed as per the SOPs at the clinical site.

Detailed RBP-6000 depot removal instructions are in Appendix 2.

6.12.2 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.

Guidance for the procedures to follow for elevated liver function tests are provided in Appendix 8.

6.12.3 Lost to Follow-up

A subject is considered as lost to follow-up if the site has made reasonable attempts to contact the subject and received no response. This may be due to the subject not returning to the site, or not answering the safety follow-up telephone call. A minimum of 2 documented telephone calls followed by a certified mailed letter is considered reasonable. At that point, the subject may be considered lost to follow-up and any open AEs may be closed.

6.12.4 Screen Failures

A screen failure subject is a subject that signed the ICF but did not receive IMP.

6.13 Other Study Procedures

6.13.1 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
- Any clinical assessments deemed appropriate for the clinical care of the subject

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

6.14 Appropriateness of Measurements

All measurements to be obtained in this study are standard and widely used.

7 STUDY ACTIVITIES

This study will be conducted as a fully non-residential (outpatient) study. An overview of the study is shown in Figure 1. Details on procedures/activities for this study are provided in Section 6 and SOE is provided in Appendix 1.

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 IMP 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, 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 may be performed by the Sponsor's (or contractor's) qualified Quality Assurance (QA) team, which is an independent function from the study conduct team. QA audits may 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 QA audits conducted at a reasonable time in a reasonable manner. Full consultation with the Investigator will be made prior to and during such a QA audit, which will be conducted according to the Sponsor's (or contractor's) QA SOPs. In addition, this study may be subject to inspections 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 must 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 the method for the analysis population and planned analyses. 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

All subjects who completed the RB-US-13-0003 study may be eligible to enroll into this study. This will be approximately 300 subjects.

9.3 Analysis Populations

The population used for all safety analyses will be comprised of all subjects who received at least 1 dose of RBP-6000 in this study.

A completer is defined as a subject who completes the EOS visit (WK 25, Day 169).

9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics (gender, race, age, weight, height) will be summarized 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

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 C-SSRS, concomitant medications; clinical laboratory results (hematology, chemistry and urinalysis); vital sign

measurements; physical examination results; body weight, height, BMI, and abdominal fat measurement (waist-to-hip ratio). Safety variables will be assessed with regards to the safety population.

Baseline is defined as the value collected at Screening. 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 after the EOS visit 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 6.9.2).

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 IMP and by severity.

9.5.1.2 Laboratory Data

Clinical laboratory assessments are conducted at screening and at the EOS visit, summary statistics for the absolute laboratory value and the change from baseline will be presented.

9.5.1.3 Vital Signs

Vital signs measurements will be assessed for clinical relevance.

9.5.1.4 Other Variables Related to Safety

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 C-SSRS scores will be summarized using descriptive statistics (mean, median, SD, minimum, maximum), including change from baseline.

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 and injection. The burning/stinging categorical variable (Yes/No) will be summarized by percent of responses for each dose.

9.6 Handling of Missing Data

Missing data will not be imputed.

9.7 Subjects Who Withdraw from the Study

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

9.8 Interim Analyses

If an interim analysis were to be performed for this study the details will be outlined in the statistical analysis plan.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

10.1.1 Sponsor

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

10.1.2 Investigational Site(s)

This study will be conducted at up to 31 sites in the US.

10.1.3 Laboratories

Laboratories used for the safety laboratory tests (serum chemistry, hematology, serology, and urinalysis), will be conducted at a central laboratory that is certified and accredited to perform the assigned assessments.

10.2 Institutional Review Board Approval

The protocol will be reviewed by an independent, appropriately constituted, centralized IRB. 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 of record has provided written approval of the protocol or a modification thereof. The IRB must be constituted and operate in accordance with the principles and requirements of ICH GCP.

IMP 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 membership list that contains member's occupations. If the IRB will not disclose the names of the committee members, the IRB Number may be accepted as a substitute for this list. Formal approval by the IRB 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 Informed Consent

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 IRB-approved ICF to review and the opportunity to ask questions. In the case of a non-medically qualified person conducting the consent process, he/she must have ready access to an investigator to whom any questions from the study subject may be referred. 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. The Investigator or the individual designated to conduct the consent discussion for the Investigator must also sign and date the ICF and the time (hour and minute) the consent is signed must be recorded. Verbal informed consent followed by a signed consent short form is not acceptable to Sponsor. Prior to participation in the study, the subject must 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 ICF 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 must not be removed from the site without subject identifiers having been redacted.

10.6 Study Monitoring

In accordance with applicable regulations, GCP, and Sponsor procedures, the CRA 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 CRA 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 must make available for direct access all study-related records upon request of the Sponsor, the Sponsor's agents, CRA, auditors, and/or IRB. The Sponsor's CRAs 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 promptly and provide the reason(s) for the suspension or termination. If the study is prematurely discontinued, all study data and IMP 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 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 clinical site. Completion of source documents will precede the completion of the eCRF. 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. Site staff will receive training on the eCRF completion guidelines and requirements for source documentation which will provided by Sponsor or its designee.

Completed eCRFs will be reviewed by the CRA in line with eCRF completion guidelines for the study to ensure completeness and consistency. The clinical monitoring plan for this study will define the level of source data verification required. 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 initialed 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 site.

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. This will include determining which deviations 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 CRA. All deviations from the protocol must 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 CRA for completeness. The subject identification and enrollment log will be treated as confidential and will be filed by the Investigator in the study center 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; IMP 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 eCRF 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 as defined in the clinical monitoring plan. 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 ICF 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

The Sponsor 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 approval of the Sponsor to do so.

11 REFERENCE LIST

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Appendix 1 Schedule of Events

Procedure/Evaluation	Screening[1]		Inj 1	Inj 2	Inj 3	Inj 4	Inj 5	Inj 6	EOS/ ET	Safety Follow-Up[15]
	EOS Visit RB-US-13-0003	Screening Visit INDV-6000-301	Day 1 Week 1	Day 29 Week 5	Day 57 Week 9	Day 85 Week 13	Day 113 Week 17	Day 141 Week 21	Day 169 Week 25	Day 197 Week 29
Window (Days)	- - - - - - - - - Same Day Events[3] - - - - - - - - -			-2 / +7	-2 / +7	-2 / +7	-2 / +7	-2 / +7	-2 / +7	-2 / +7
Informed Consent [2]		X								
IWRS		X	X	X	X	X	X	X	X	
Demographics		X								
Medical History		X								
Inclusion / Exclusion Criteria		X								
Vital Signs [4]	X		X [5]	X	X	X	X	X	X	
Urine Pregnancy Test [6]	X			X	X	X	X	X	X	
Urine Drug Screen [7]	X			X	X	X	X	X	X	
AE Assessment	X		X	X	X	X	X	X	X	X
Concomitant Medications	X		X	X	X	X	X	X	X	X
C-SSRS [8]	X	X		X	X	X	X	X	X	
Injection Site Evaluation [9]	X			X	X	X	X	X	X	
RBP-6000 Injection			X	X	X	X	X	X		
Injection Site Grading Scale [10]			X	X	X	X	X	X		
Injection Site Pain VAS [10]			X	X	X	X	X	X		
Counseling / Behavioral Therapy	X			X	X	X	X	X	X	
Review of Treatment Options[12]							X	X	X	
Physical Examination[13]	X								X	
Body Weight	X								X	
Height		X								
BMI (calculated in CRF)		X							X	
Hip and Waist Circumference	X								X	
Hip-to-Waist Ratio (calculated in CRF)		X							X	

Procedure/Evaluation	Screening[1]		Inj 1	Inj 2	Inj 3	Inj 4	Inj 5	Inj 6	EOS/ ET	Safety Follow-Up[15]
	EOS Visit RB-US-13-0003	Screening Visit INDV-6000-301	Day 1 Week 1	Day 29 Week 5	Day 57 Week 9	Day 85 Week 13	Day 113 Week 17	Day 141 Week 21	Day 169 Week 25	Day 197 Week 29
Window (Days)	- - - - - - - - - Same Day Events[3] - - - - - - - - -			-2 / +7	-2 / +7	-2 / +7	-2 / +7	-2 / +7	-2 / +7	-2 / +7
Hematology / Serum Chemistry [14]	X								X	
Urinalysis [14]	X								X	

AE = adverse event; BMI = body mass index; C-SSRS = Columbia Suicide Severity Rating Scale; EOS = End of Study; ET = Early Termination; Inj. = injection; IWRS=Interactive voice/web response system; NA = Not Applicable; VAS = Visual Analog Scale.

1. All indicated screening assessments conducted during the RB-US-13-0003 EOS Visit will be used as part of the overall screening process for the present study. However, required assessments indicated under "Screening Visit INDV-6000-301" must only be performed after the ICF is signed.
2. The ICF may be shared with the subject up to 2 months before the EOS Visit for RB-US-13-0003 study in order to discuss this new study as a possible treatment option. However, the ICF for this study must not be signed until all assessments for the RB-US-13-0003 EOS Visit are complete.
3. The Screening Visit assessments and Day 1 injection must occur on the same day as the RB-US-13-0003 EOS Visit.
4. Includes blood pressure, pulse oximetry, pulse rate, respiratory rate, and oral temperature which must be taken after subject is supine ≥ 3 minutes. With the exception of Day 1, vital signs will be taken ≤ 60 minutes prior to injection, and 1 hour (± 30 minutes) post-completion of injection.
5. On Day 1, vital signs are only required to be collected 1 hour (± 30 minutes) post-completion of injection; the screening value will serve as the pre-injection value.
6. Only for female subjects who are of childbearing potential (not postmenopausal or surgically sterile for at least 1 year).
7. Oxycodone may not show up in all opiate assays and should be assessed separately.
8. At the EOS Visit for Study RB-US-13-0003, the C-SSRS "since last visit" (e-PRO) version will be used for confirming exclusion 3 only. In addition, as part of the Screening Visit for INDV-6000-301, the C-SSRS "baseline/screening" (paper) version will be required to be completed; on all other visits, the "since last visit" (paper) version should be used. The C-SSRS "baseline/screening" assessment will include both a lifetime and past 6-month time interval.
9. Injection site will be evaluated for potential reaction and evidence of attempted removal before the next injection of RBP-6000 is administered.
10. Local injection site grading will be performed 1 hour (± 30 minutes) post-completion of injection.
11. Injection Site Pain VAS will be completed by the subject 1 hour (± 30 minutes) post-completion of injection.
12. Subject's alternative treatment options should be assessed at least two months before EOS, however it is recommended to review at each visit.
13. Brief physical examination including general appearance, chest/lungs, heart, abdomen and a brief neurological assessment.
14. Additional unscheduled labs may be added at the Investigator's discretion in order to fully assess any AEs.
    All subjects should receive a safety follow-up contact. Subjects should be contacted by telephone in order to inquire about any new AEs, or a stop date for any ongoing AEs or concomitant medications. They are not required to return to the site, unless the Investigator deems it medically necessary. 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 will be considered a reasonable effort for contacting the subject. If follow-up contact with a subject cannot be made, any open AEs will be designated as "ongoing."

Appendix 2 IMP 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 IMP. 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- or 5/8-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.

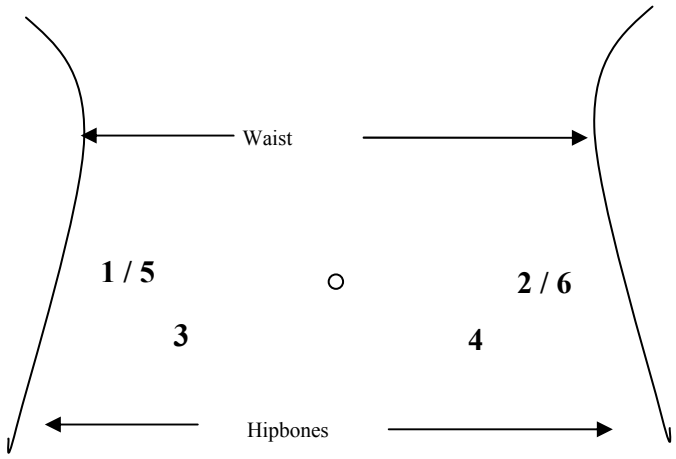
Administration Procedure:

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 2. Injections should be started based on where the last injection in RB-US-13-0003 was given.

Figure 2 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 the needle quickly. If a 1-inch needle is used, enter half the length, if a 5/8-inch needle is used the needle may be inserted fully. 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 non-dominant 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 dispose of syringe and needle in an appropriate waste 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. Dispose of used and unused syringe and needle in an appropriate waste 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 clinical site.

Appendix 3 Prohibited Cytochrome P450 Inhibitors and Inducers

Cytochrome P450 3A4 Inhibitors			
Name	**Example Brand Name(s)**	**Name**	**Example Brand Name(s)**
Amiodarone	Cordarone, Nexterone	Ketoconazole	Nizoral
Amprenavir	Agenerase,	Metronidazole	Flagyl
Aprepitant	Emend	Mibefradil	Posicor
Chloramphenicol	Chloromycetin	Miconazole	Oravig
Cimetidine	Tagamet	Mifepristone	Mifeprex, Korlym
Ciprofloxacin	Ciloxan, Cipro	Nefazodone	Serzone
Clarithromycin	Biaxin	Nelfinavir	Viracept
Clotrimazole	Lotrimin	Nicardipine	Cardene
Cyclosporine	Neoral, Sandimmune	Norfloxacin	Noroxin
Delavirdine	Rescriptor	Norfluoxetine	Seproxetine (discontinued)
Diethyl-dithiocarbamate	(zinc chelator used in cancer, no other name)	Propofol	Diprivan
Diltiazem	Cardizem, Dilacor	Quinine	Qualaquin
Ethinyl estradiol	Apri, Aviane, Beyaz	Ritonavir	Norvir
Erythromycin	Erythrocin	Saquinavir	Invirase
Fluconazole	Diflucan	Sertraline	Zoloft
Fluoxetine	Prozac	Starfruit	Carambola, fruit of Averrhoa carambola
Fluvoxamine	Luvox	Telithromycin	Ketek
Gestodene	Progestogen hormonal contraceptive. Not available in the US.	Troleandomycin	Not available in the US
Grapefruit juice	Grapefruit juice	Verapamil	Isoptin
Imatinib	Gleevec	Voriconazole	Vfend
Indinavir	Crixivan	Zafirlukast	Accolate
Itraconazole	Sporanox		

Cytochrome P450 3A4 Inducers			
Name	**Example Brand Name(s)**	**Name**	**Example Brand Name(s)**
Barbiturates	Nembutal, Luminal	Phenytoin	Dilantin, Phenytek
Carbamazepine	Carbatrol, TEGretol	Pioglitazone	Actos
Dexamethasone	Decadron	Primidone	Mysoline
Efavirenz	Sustiva, Atripla	Rifabutin	Mycobutin
Ethosuximide	Zarontin	Rifampin	Rifadin, Rimactane
Glucocorticoids	Prednisone, Medrol, Millipred	Hypericum perforatum	Medicinal herb
Glutethimide	Doriden (Not available in US), Elrodorm, Noxyron.	Sulfadimidine	Not available in the US
Modafinil	Provigil	Sulfinpyrazone	Anturane
Nevirapine	Viramune	Troglitazone	Rezulin, Resulin Non available in US
Oxcarbazepine	Trileptal, Oxtellar XR	Troleandomycin	Tao Not available in the US
Phenobarbital	Luminal		

Cytochrome P450 2C8 Inhibitors			
Name	**Example Brand Name(s)**	**Name**	**Example Brand Name(s)**
Gemifibrozil	Lopid	Montelukast	Singulair
Trimethoprim	Primsol, Proloprim	Quercetin	Plant pigment (flavonoid)
Glitazones	Actos, Avandia		

Cytochrome P450 2C8 Inducer			
Name	**Example Brand Name(s)**	**Name**	**Example Brand Name(s)**
Rifampicin	Rifadin		

Source: http://medicine.iupui.edu/clinpharm/ddis/clinical-table/ Accessed 30 September 2016.

Appendix 4 Columbia Suicide Severity Rating Scale (C-SSRS) -- Baseline/Screening Version

SUICIDAL IDEATION		
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.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts 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. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act 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."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
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. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (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	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***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?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***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?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** 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. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***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)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* 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. ***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?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: 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. ***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?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: 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). ***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)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 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; *medical* 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; *medical* 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* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 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* _____	*Enter Code* _____

Note: Screening assessment should include both a lifetime and "past 6-month" time interval.

Appendix 5 Columbia Suicide Severity Rating Scale (C-SSRS) -- Since Last Visit Version

SUICIDAL IDEATION	
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
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts 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. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act 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."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
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:*** ___ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (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	___
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___
Deterrents ***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?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___
Reasons for Ideation ***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?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, 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. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***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)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* 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. ***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?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: 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. ***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?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: 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). ***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)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 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; *medical* 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; *medical* 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* _____
Potential Lethality: Only Answer if Actual Lethality=0 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* _____

Appendix 6 Injection Site Grading Scale

Injection site Reactions	None (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (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 30 September 2016.

Appendix 7 Injection Site Pain Visual Analog Scale

How would you rate your injection site pain today?

No Pain _____ Pain as bad 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 ☐

Note: Copies of any pre-printed VAS forms to be completed by a subject must be checked to confirm that the rating scale measures 100 mm (3.94 in) in length.

Appendix 8 Elevated Liver Function Tests

Elevated liver functions tests meeting one of the following criteria below must follow the outlined procedures.

Criteria 1

ALT ≥3X ULN and <5X ULN
+ Bilirubin <2X ULN
+ DO NOT exhibit hepatitis symptoms or rash

- Contact the Indivior Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety.
- Subject may continue study treatment, if liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) can be monitored weekly for up to 4 weeks.
- If the subject later meets criteria 2 or 3, immediately withdraw study treatment, perform additional testing and continue safety follow–up until liver chemistries resolve, stabilize or return to baseline values.
- After 4 weeks of monitoring, if ALT <3XULN and bilirubin <2XULN, subject must be monitored twice monthly until liver chemistries normalize or return to within baseline values.

Criteria 2

ALT ≥5X ULN
or
ALT ≥3X ULN
+ Hepatitis symptoms or rash
+ cannot be monitoring for 4 weeks or have elevations that persist ≥4 weeks

- Subject must not receive any further injections of RBP-6000.
- Contact the Indivior Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety and any addition laboratory testing required.
- Make every reasonable attempt to have the subject return to the clinic within 24-72 hours for repeat liver chemistries and additional testing.
- Monitor subject weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

- Upon completion of the safety follow-up, the subject must be withdrawn from the study unless further follow–up is required.

Criteria 3

ALT ≥3X ULN + Bilirubin ≥2X ULN (>35% direct)
or
ALT ≥3X ULN + INR >1.5:

Note: INR testing is not required per protocol and the threshold value does not apply to subjects receiving anticoagulants.

- Subject must not receive any further injections of RBP-6000.
- Contact the Indivior Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety and any addition laboratory testing required.
- Make every reasonable attempt to have the subject return to the clinic within 24 hours for repeat liver chemistries, additional testing and close monitoring (with specialist or hepatology consultation recommended).
- Monitor the subject twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.
- Upon completion of the safety follow-up, the subject must be withdrawn from the study unless further follow–up is required.

Appendix 9 Sponsor Signatures

Study Title:	An Open-Label, Depot Buprenorphine (RBP-6000) Treatment Extension Study in Subjects with Opioid Use Disorder
Study Number:	INDV-6000-301
Original Protocol:	24 June 2016
Amendment 1:	30 September 2016

This clinical study protocol was subject to critical review and has been approved by the Sponsor.

Signed: [redacted] Date: 9/30/16

Head Late Stage Development, Global Clinical Development
Indivior Inc.

Signed: [redacted] Date: 09/30/2016

Medical Monitor
Indivior Inc.

Appendix 10 Investigator's Signature

Study Title:	An Open-Label, Depot Buprenorphine (RBP-6000) Treatment Extension Study in Subjects with Opioid Use Disorder
Study Number:	INDV-6000-301
Original Protocol:	24 June 2016
Amendment 1:	30 September 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: