16.1.1 CLINICAL RESEARCH PROTOCOL

DRUG:	SUBLOCADE (RBP-6000)
STUDY NUMBER:	INDV-6000-401
PROTOCOL TITLE:	A Randomised, Double-Blind Study Comparing 2 Maintenance Dosing Regimens of Buprenorphine Extended-Release Subcutaneous Injection (RBP-6000) in Treatment-Seeking Adult Participants with Opioid Use Disorder and High-risk Opioid Use
SHORT PROTOCOL TITLE:	Transform Study TReating AddictioN in high risk population with Sublocade FOR Maintenance
PHASE:	IV
IND NUMBER:	107,607
SPONSOR:	Indivior Inc. 10710 Midlothian Turnpike, Suite 125 North Chesterfield, VA 23235 USA
AMENDMENT 3 PROTOCOL DATE:	07 Apr 2022 (Version 4.0)

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title:	A Randomised, Double-Blind Study Comparing 2 Maintenance Dosing Regimens of Buprenorphine Extended-Release Subcutaneous Injection (RBP-6000) in Treatment-Seeking Adult Participants with Opioid Use Disorder and High-risk Opioid Use
Protocol Number:	INDV-6000-401
Amendment 3 Date:	07 Apr 2022 (Version 4.0)

This clinical study protocol was subject to critical review and has been approved by the appropriate protocol review committee of Indivior. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational medicinal product.
- The moral, ethical and scientific principles governing clinical research as set out in the principles of International Council on Harmonisation (ICH) E6 (Good Clinical Practice) and according to applicable local laws and regulations.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational medicinal product.

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

Protocol Title: A Randomised, Double-Blind Study Comparing 2 Maintenance Dosing Regimens of Buprenorphine Extended-Release Subcutaneous Injection (RBP-6000) in Treatment-Seeking Adult Participants with Opioid Use Disorder and High-risk Opioid Use

Protocol Number: INDV-6000-401

Amendment 3 Date: 07 Apr 2022 (Version 4.0)

The information contained in this protocol and all other information relevant to this investigational medicinal product is the confidential and proprietary information of Indivior, and except as may be required by local laws or regulation, may not be disclosed to others without prior written permission of Indivior.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. My staff and/or I will conduct this study as outlined herein, in accordance with the regulations stated in the International Council on Harmonisation E6 / Good Clinical Practice (ICH/GCP) guidelines and will make a reasonable effort to complete the study within the time designated.

I agree to ensure all associates, colleagues and employees delegated to assist with the conduct of the study are trained on this study protocol and amendments, other study-related materials and are qualified to perform their delegated tasks. I will provide all study personnel copies of the protocol and any amendments and grant access to all information provided by Indivior or specified designees. I will discuss the material with them to ensure that they are fully informed about RBP-6000 and appropriate information throughout the study. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

STUDY PERSONNEL INFORMATION

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History	
Document:	**Date**
Amendment 3	07 Apr 2022
Amendment 2	31 Jan 2022
Amendment 1	15 Jul 2021
Original Protocol	26 Jan 2021

Amendment 3 (07 Apr 2022)

This amendment is created because it affects the selection, the criteria for selection, monitoring, and dismissal of a clinical trial subject.

Rationale for the Amendment:

[redacted]

Section Number and Name	Description of Change	Brief Rationale
[redacted]		

STUDY SUMMARY

Protocol Title:

A Randomised, Double-Blind Study Comparing 2 Maintenance Dosing Regimens of Buprenorphine Extended-Release Subcutaneous Injection (RBP-6000) in Treatment-Seeking Adult Participants with Opioid Use Disorder and High-risk Opioid Use

Protocol Number:

INDV-6000-401

Rationale:

[redacted]

[redacted]

Target Population:

Treatment-seeking individuals at least 18 years of age with moderate to severe OUD, as assessed by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria, who are currently either:

a. Using opioids via the injection route for an average of 5 or more days per week in the last 4 weeks

b. using at least 500 mg intravenous (IV) heroin equivalent (e.g., 1250 mg IV morphine) or self-reported use of any dose of highly potent synthetic opioids (fentanyl and analogues excluding transdermal patches) for an average of 5 or more days per week in the last 4 weeks by any route (See Appendix 22.8, Morphine Dose Analgesic Equivalence Table).

Number of Participants:

Approximately 489 participants will be enrolled and receive RBP-6000 treatment, to ensure there are enough participants remaining following the initial open-label RBP-6000 treatment period to randomise N=390 participants; [redacted]

Objectives

The primary objective of this study is to compare the efficacy of 100-mg and 300-mg maintenance doses of RBP-6000 administered every 4 weeks in participants who use opioids via an injection route and/or use high doses of opioids.

The secondary objective of this study is to assess the effect of 100-mg and 300-mg maintenance doses of RBP-6000 administered every 4 weeks on treatment retention and parameters of harm reduction (i.e., frequency of opioid use) in participants who use opioids via an injection route and/or use high doses of opioids.

[redacted]

[redacted]

The safety objective of this study is to assess the safety and tolerability of RBP-6000 in participants who use opioids via an injection route and/or use high doses of opioids.

Open-label Induction Sub-study

The primary objective of the sub-study is to compare treatment retention of participants following rapid induction or SoC induction onto RBP-6000.

The secondary objective of the sub-study is to evaluate the safety and tolerability of RBP-6000 in participants during the Open-label Induction Sub-study.

[redacted]

Study Design:

This randomised, double-blind, parallel group, multicentre study will compare the efficacy, safety and tolerability of 100mg and 300mg maintenance doses of RBP-6000 administered every 4 weeks to high-risk, treatment-seeking adult participants with moderate to severe OUD (as assessed by DSM5) who use opioids via an injection route and/or use high doses of opioids. An Open-label Induction Sub-study is nested within this study and will compare treatment retention and safety and tolerability of RBP-6000 in participants following rapid induction or SoC induction.

Participants who provide written informed consent will be assessed for eligibility during an up to 30-day Screening Period. During Screening, the Investigator will ask the participant to self-report recent drug use (including the use of a TimeLine Follow Back [TLFB]) to assess eligibility for high-risk opioid use. Eligibility will be assessed by the participants' TLFB only, and the Investigator may discuss any positive UDS results with the participant only after the completion of the TLFB.

Participants determined to be eligible will be advised to abstain from short-acting opioids (such as morphine sulphate, oxycodone, hydromorphone, oxymorphone or codeine) for at least 6 hours, and long-acting opioids (such as methadone or levorphanol) for at least 24 hours, before arriving at the site for TM buprenorphine induction. Participants will be informed that under-reporting their last use of opioids and undergoing induction with remaining exposure to opioids places them at high risk for rapid and intense onset of withdrawal symptoms. This risk is increased with high doses of potent opioids, such as fentanyl, which may take longer to clear due to high lipophilicity, redistribution into fat, and prolonged excretion patterns (Mariani 2020). An on-site dipstick UDS at Screening to identify current opioids of abuse will support discussion between the Investigator and study participant about the optimal period of abstinence before starting induction.

[redacted]

[redacted]

Eligible participants may complete the induction visit once all inclusion and exclusion criteria are confirmed, including applicable laboratory assessments.

Approval from the sponsor must be obtained for any local laboratory and the laboratory normal ranges utilized to determine eligibility for screening. If a local laboratory is utilized for eligibility, the laboratory samples will also be sent to the central laboratory for the baseline analysis value.

If eligibility is confirmed at the screening visit, participants may complete the induction visit. Participants having same-day screening and induction visits are not required to repeat the UDS, pregnancy test, vitals, and ECG for the induction visit.

On induction days, eligible participants will provide a urine sample for a UDS dipstick and pregnancy test (female participants of child-bearing potential only). If a female participant has a positive pregnancy test, she will be discontinued and will not proceed with subsequent assessments. The Investigator will ask him/her to self-report recent drug use (including the use of a TLFB). The Investigator may discuss any positive UDS results with the participant only after completion of the TLFB.

Participants who report that they have used long-acting opioids within the previous 24 hours will not be permitted to proceed with induction until the 24-hour period has passed. If necessary, induction may be rescheduled. The 1st day of the repeat induction should be scheduled within 30 days of informed consent. Participants who have used short-acting opioids within the previous 6 hours may be permitted to proceed with the induction visit at the discretion of the Investigator. All concomitant medications used since Screening will be reviewed.

When the participant has met the TM buprenorphine dosing criteria, he/she will be randomised at a 2:1 ratio to RBP-6000 rapid induction or SoC induction. Due to the potential for fentanyl use to impact the response to TM buprenorphine induction, randomisation will be stratified according to the same-day UDS result for fentanyl (negative or positive). The rapid induction arm is designed to initiate RBP-6000 treatment following a single dose of TM buprenorphine, while the SoC induction arm inducts the participant onto RBP-6000 using a TM buprenorphine containing product for a minimum of 7 days.

If the participant displays any allergic/hypersensitivity reaction to TM buprenorphine, the participant will be discontinued from the study.

Following TM buprenorphine induction using either rapid induction or SoC induction, and confirmation that the participant is eligible for dosing with RBP-6000, pre–RBP-6000 assessments will be conducted; if eligible, 300 mg RBP-6000 may be administered SC and the visit will be considered Day 1.

Following the first injection of RBP-6000 (300 mg), the participants will remain at the site for at least 4 hours after the injection and be monitored for safety and tolerability.

If the participant experiences exacerbated withdrawal symptoms at any time (including precipitated withdrawal), he/she may be treated symptomatically per the SAMHSA TIP 63

2020 guidelines:

- Nausea: ondansetron or metoclopramide
- Diarrhoea: loperamide
- Anxiety, irritability, sweating: clonidine
- Insomnia: diphenhydramine, trazodone
- Pain: Nonsteroidal anti-inflammatory drugs

For participants in the rapid induction arm, following the first injection of 300 mg RBP 6000, TM buprenorphine in increments of 2 to 4 mg up to a maximum dose of 12 mg (inclusive of pre–RBP-6000 TM buprenorphine) may be administered on Day 1 at the discretion of the Investigator to alleviate withdrawal symptoms while on site. Regardless of induction arm, participants are not permitted to take home supplemental TM buprenorphine after RBP-6000 is administered.

The second RBP-6000 dose will be administered at Week 2, 1 week (+4 days) after the first injection.

Participants will be followed up via telephone the day after the first and second RBP-6000 injections.

Participants eligible to continue treatment will be randomised at Week 6 prior to Injection 3 in a 1:1 ratio to receive maintenance doses of either 300 mg or 100 mg every 4 weeks (-2/+4 days) for a total of up to 8 maintenance injections. Randomisation prior to the third RBP-6000 dose will be stratified according to opioid use predominantly via injection route at Screening (yes or no) and Week 6 UDS result for opioids (negative or positive).

Participants will return to the site for weekly UDS and collection of self-reported drug use, including TLFB, from Weeks 1 to 10. From the fourth injection until the end of the treatment period (Weeks 10 to 38), UDS and self-reported drug use, including TLFB, will be obtained at every injection visit. In addition, random visits to assess UDS and TLFB (only) will be scheduled by the Investigator in between every injection (2 weeks post each injection ±7 days) from Injection 4 through Injection 10. All participants will receive counselling, per SoC, from Day 1, Week 1, through the end of the treatment period.

All participants will continue study treatment until they complete the end-of-treatment (EOT) Visit (Week 38). Participants who prematurely discontinue RBP-6000 treatment will complete the early termination (ET) visit. During the last injection visit (Week 34) through the EOT visit (or the ET for those who prematurely discontinue), the Investigator or a medically qualified sub-Investigator will discuss available options for continued treatment. Any participant with ongoing adverse events (AE) at the EOT or ET visit will also be followed up by phone 2 weeks later for the End of Study (EOS) visit to assess any ongoing AEs and concomitant medications associated with those ongoing AEs only.

No dose increases or decreases of RBP-6000 are allowed.

Primary Efficacy Endpoint

The proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 20 to 38 (inclusive).

Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- participants' percentage of days opioids were used out of days assessed (TLFB) over Weeks 10 to 38 (inclusive).
- proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 10 to 38 (inclusive)
- participants' percentage of visits with opioid abstinence (defined as negative UDS and TLFB for opioid use) over Weeks 10 to 38 (inclusive)
- proportion of responders for weekly opioid use, defined as participants' percentage of visits with opioid abstinence being greater than or equal to 80% for the last 5 visits planned for UDS and TLFB assessment over Week 30 to Week 38.
- proportion of responders for daily opioid use, defined as participants' percentage of days opioids were used out of days assessed (TLFB) being less than or equal to 20% for participants' last 5 visits with observed TLFB post randomisation.
- participants' percentage of visits with opioid abstinence (defined as negative UDS and TLFB for opioid use) overall (Week 2 to 38 inclusive)
- participants' percentage of days opioids were used out of days assessed (TLFB) overall (Week 2 to 38 inclusive)
- for participants who use opioids via the injection route for an average of 5 or more days per week in the last 4 weeks prior to Screening, participants' percentage of days opioids were used via the injection route out of days assessed (TLFB) overall (Weeks 10 to 38 inclusive)
- average number of times opioids were used per week (TLFB) by visit
- change in participants' number of times opioids were used per week from Screening or randomisation baseline to each visit
- proportion of participants abstinent (defined as negative UDS and TLFB for opioid use) by visit
- average number of days opioids were used per week (TLFB) by visit
- treatment retention since randomisation
- proportion of randomised participants who complete the last scheduled injection of RBP-6000

Exploratory Efficacy Endpoints

[redacted]

[redacted]

Safety Assessments/Endpoints

Major safety endpoints include the proportion of participants with at least 1 treatment-emergent AE (TEAE) of the following types at any time during the treatment period: any TEAE, drug-related TEAE, treatment-emergent serious AE (SAE), drug-related treatment-emergent SAE, or TEAE leading to treatment discontinuation. Additional safety endpoints include assessment of laboratory results, vital signs and concomitant medications. Participants will be contacted by phone the day following Injections 1 and 2 to ask about AEs and concomitant medication use.

Open-label Induction Sub-study Endpoints

The primary endpoint of this sub-study is treatment retention at Injection 2, defined as the proportion of participants receiving Injection 2 at the Week 2 visit among those who received at least 1 dose of TM buprenorphine for induction and did not demonstrate idiosyncratic response to the first dose of TM buprenorphine.

The secondary endpoints of this sub-study are the following:

- time to treatment discontinuation from the first dose of TM buprenorphine used for induction during the Open-label Treatment Period (OLTP), defined as the number of days from the first dose of TM buprenorphine until the last scheduled visit observed during the OLTP. Participants receiving the third RBP-6000 injection (i.e., the first randomised injection) will be censored administratively at the end of the OLTP; otherwise participants will be viewed as having discontinued treatment at their last scheduled visit observed during the OLTP. Participants discontinued due to idiosyncratic response to the first dose of TM buprenorphine will not be included.
- adverse events up to Injection 2, and between Injections 2 and 3

[redacted]

[redacted]

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LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
COWS	Clinical Opiate Withdrawal Scale
CRF	case report form
DBTP	Double-Blind Treatment Period
[redacted]	[redacted]
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
[redacted]	[redacted]
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
[redacted]	[redacted]
IA	interim analysis
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IE	intercurrent events
IEC	Independent Ethics Committee
IES	intercurrent events strategy

INR	international normalised ratio
IRB	Institutional Review Board
IV	intravenous(ly)
IXRS	Interactive Voice/Web Response System
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MOUD	medications for opioid use disorder
msec	millisecond
[redacted]	[redacted]
n	number of participants
NI	non-inferiority
[redacted]	[redacted]
OLTP	Open-label Treatment Period
OUD	opioid use disorder
[redacted]	[redacted]
Ph3DB	Phase III double-blind (study) – RB-US-13-0001
[redacted]	[redacted]
PLGH	poly(DL-lactide-co-glycolide) with a carboxylic acid end group
QTcF	corrected QT – Fridericia's
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SEP	Sub-study Enrolled Population
SFAS	Sub-study Full Analysis Set
SoC	standard of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
TLFB	TimeLine Follow Back

TM	transmucosal
UDS	urine drug screen
ULN	upper limit of normal
USA	United States of America
WHO	World Health Organization
[redacted]	[redacted]
[redacted]	[redacted]

1 INTRODUCTION AND RATIONALE

1.1 Background

Opioid use disorder (OUD) is a neurobehavioral syndrome characterised by repeated, compulsive seeking or use of an opioid despite adverse social, psychological and physical consequences (SAMHSA 2004). This chronic, relapsing disease has grown to epidemic proportions. The clinical course of OUD typically includes periods of exacerbation and remission, but the patient is never disease-free. A combination of counselling/behavioural therapy with medications for OUD (MOUD) provides for a whole-patient approach and is recommended by treatment guidelines as the current standard of care (SoC) for OUD. (Kampman 2015).

SUBLOCADE® (extended-release buprenorphine) injection (RBP-6000), for subcutaneous (SC) use (CIII) is currently indicated for the treatment of moderate to severe OUD in patients who have initiated treatment with a transmucosal (TM) buprenorphine containing product for a minimum of 7 days to suppress opioid withdrawal signs and symptoms (SUBLOCADE prescribing information) in the United States of America (USA) and for similar indications in other regions. SUBLOCADE is administered once monthly (i.e., every 4 weeks) by SC injection and provides sustained plasma levels of buprenorphine, a mu opioid- receptor partial agonist, over the dosing interval. SUBLOCADE uses buprenorphine and the ATRIGEL® Delivery System, which consists of a biodegradable poly(DL-lactide-co-glycolide) with a carboxylic acid end group (PLGH) polymer, dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone. SUBLOCADE is injected as a solution, and subsequent precipitation of the polymer creates a solid depot containing the buprenorphine. After initial formation of the depot, buprenorphine is released via diffusion from, and the biodegradation of, the depot. SUBLOCADE should be used as a part of a complete treatment programme that includes counselling and psychosocial support.

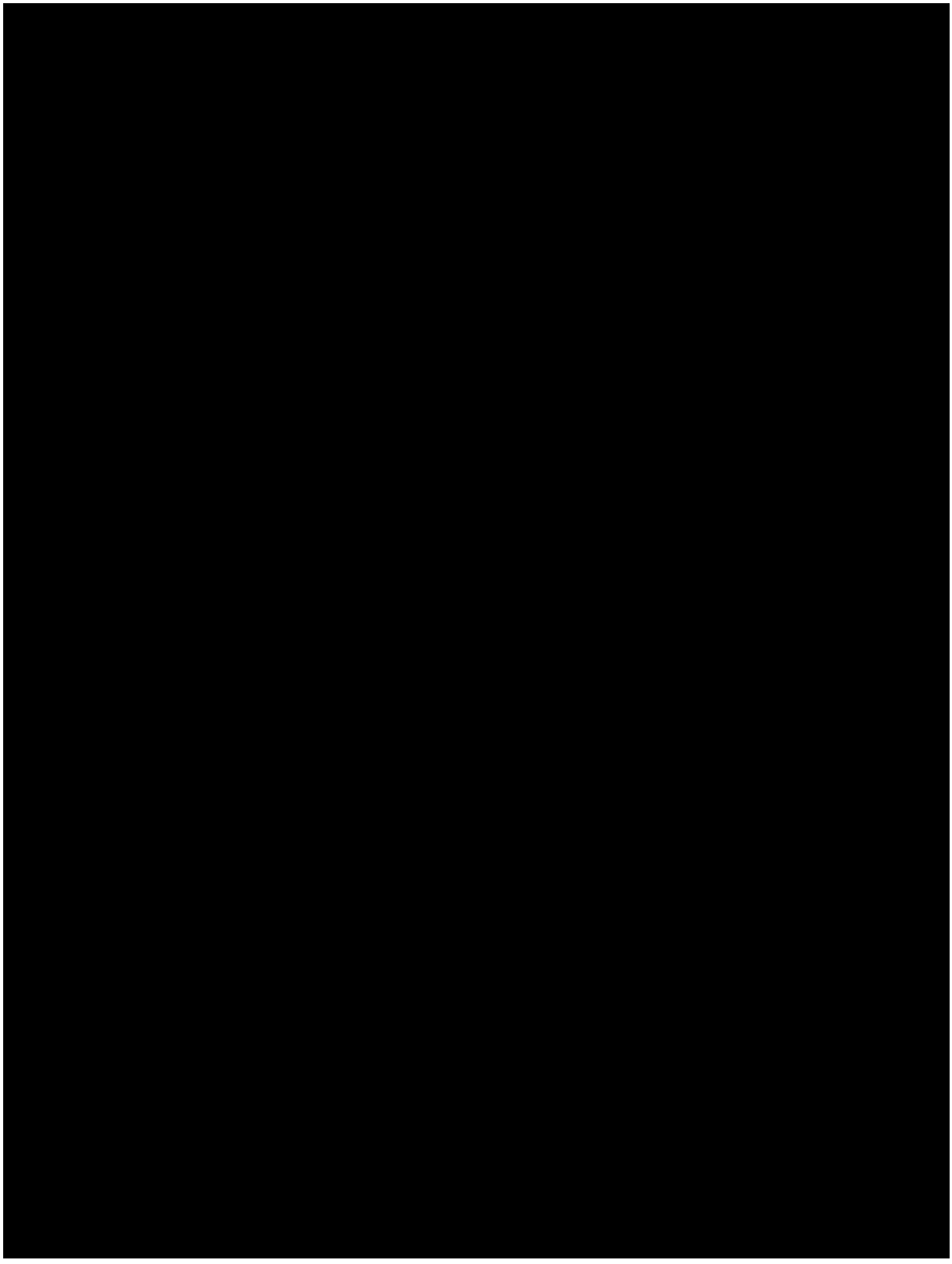
Approval of SUBLOCADE by the USA Food and Drug Administration (FDA) in 2017 was based in part on results of a pivotal Phase III double-blind, placebo-controlled study (Ph3DB; RB-US-13-0001; NCT02357901). That study evaluated 2 dosing regimens of SUBLOCADE: 2 monthly doses of 300 mg followed by 4 monthly doses of 300 mg (300/300-mg regimen), and 2 monthly doses of 300 mg followed by 4 monthly doses of 100 mg (300/100-mg regimen). The primary efficacy endpoint of the pivotal Ph3DB study was participants' percentage abstinence from opioid use (based on urine drug screening [UDS] and self-reports) from Week 5 to Week 24. Both the 300/300-mg and 300/100-mg SUBLOCADE regimens showed higher participants' percentage abstinence compared with the placebo group (300/300 mg: 41%; 300/100 mg: 43%; placebo: 5%; $P<0.0001$). The key secondary endpoint was treatment success, defined as any participant with >80% abstinence from opioid use between Week 5 and Week 24. The

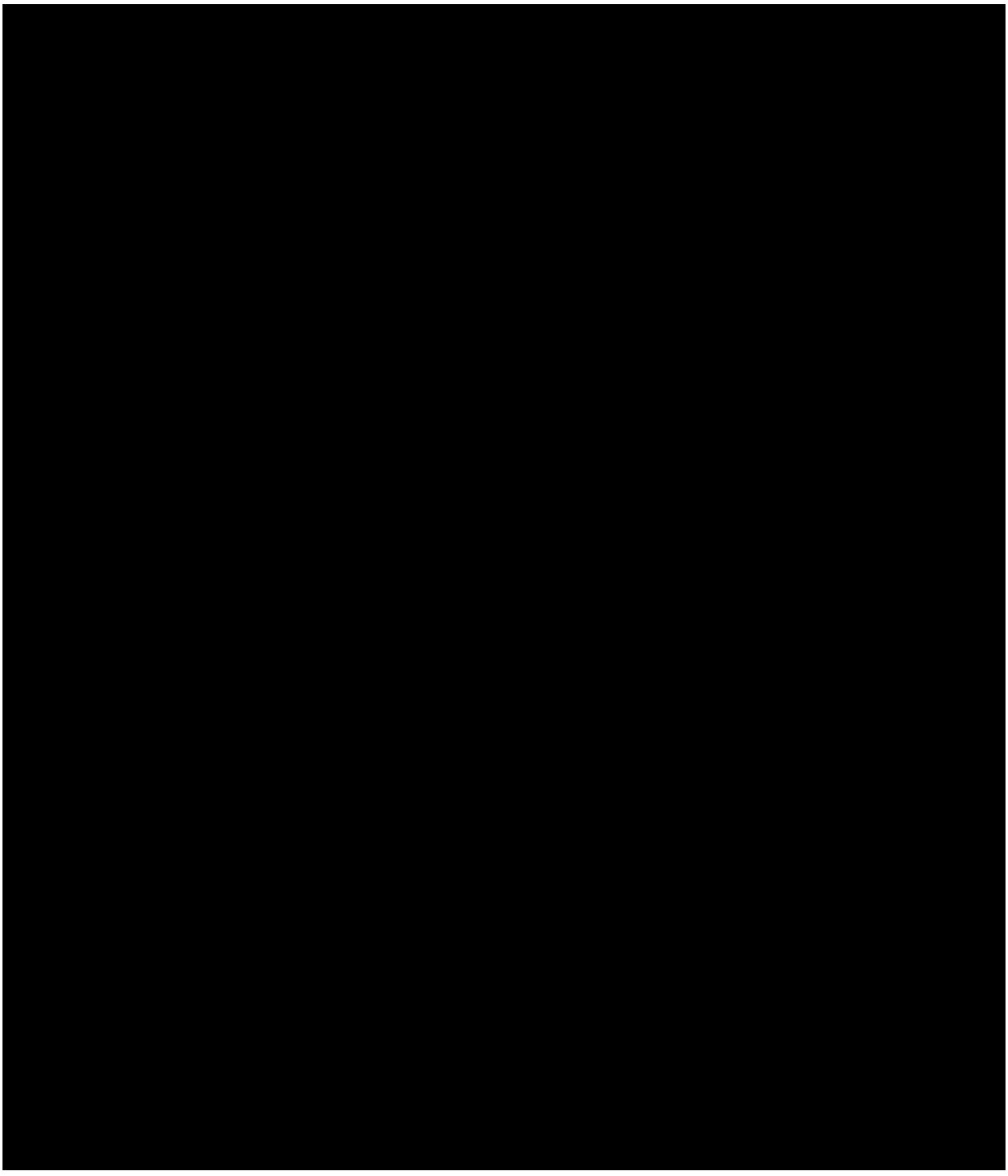
SUBLOCADE groups had higher proportions of participants who achieved at least 80% abstinence compared with the placebo group (300/300 mg: 29%; 300/100 mg: 28%; placebo: 2%; P<0.0001).

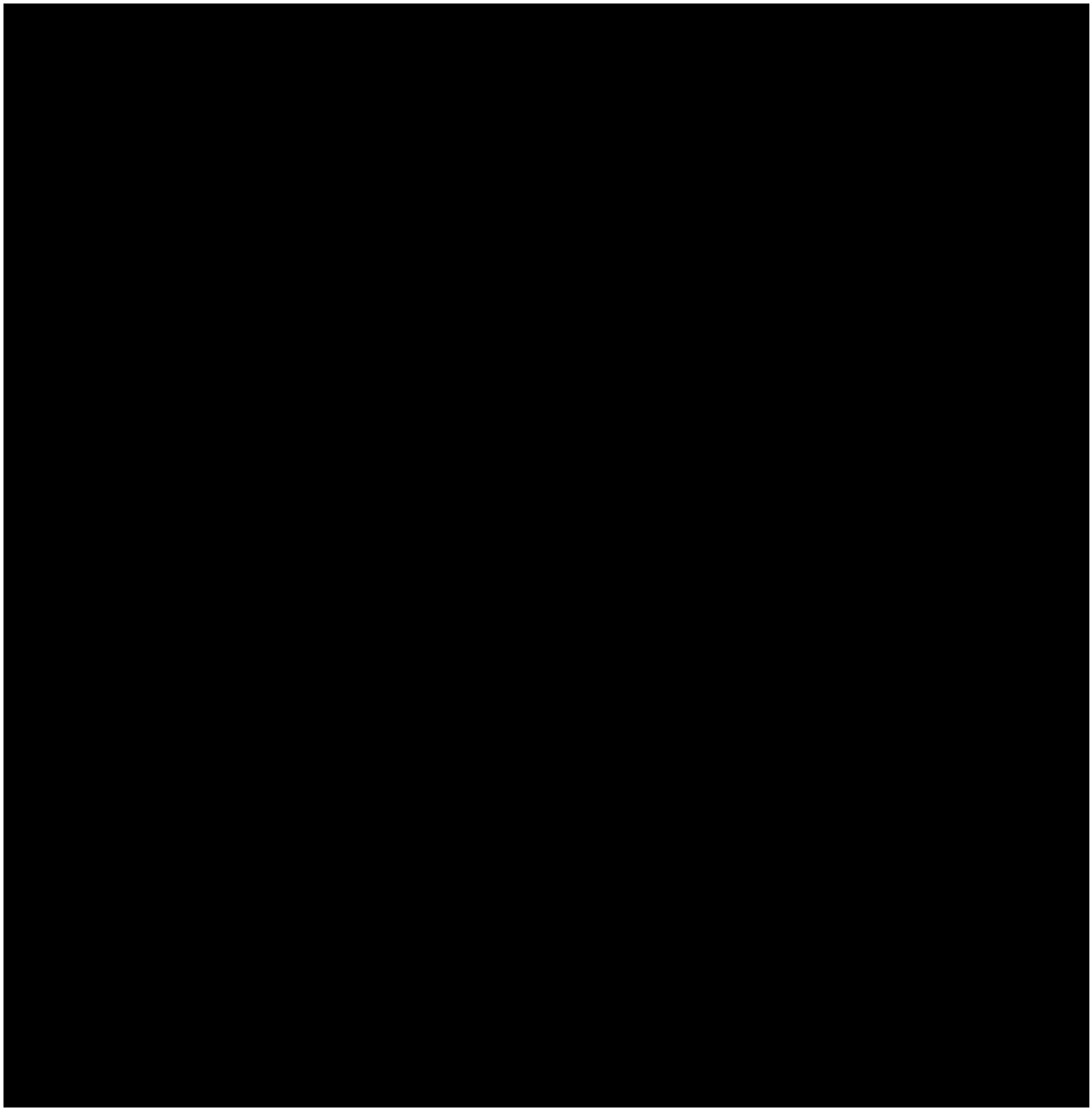
The recommended dose of SUBLOCADE is 300 mg monthly for the first 2 months followed by monthly 100-mg maintenance doses; increasing the monthly maintenance dose to 300 mg may be considered for patients who tolerate the 100-mg dose, but do not demonstrate a satisfactory clinical response, as evidenced by self-reported opioid use or UDS positive for opioid use. This current study is designed to evaluate differences between the 100-mg and 300-mg maintenance doses in participants predicted to benefit from the higher 300-mg maintenance dose based on their historical pattern of high-risk drug use, and to further describe the benefits and risks of the 300-mg and 100-mg maintenance doses. “High-risk opioid use” as defined in this protocol includes use of opioids for an average of 5 or more days per week in the last 4 weeks either via the injection route or at quantities of at least 500 mg intravenous (IV) heroin equivalent, which is consistent with the definition of high-risk drug use provided by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA 2014). Because quantitation of heroin equivalent is challenging to estimate, self-reported use of any dose of highly potent synthetic opioids (fentanyl and analogues excluding transdermal patches) was added.

The study will be carried out in accordance to the protocol and with local legal and regulatory requirements, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP) and all applicable participant privacy requirements.

1.2 Study Rationale







1.3 Risk-Benefit Assessment

Buprenorphine is a partial agonist at the mu-opioid receptor. As such, it produces a submaximal pharmacological response compared with that of a full agonist at these receptors and provides a greater margin of safety with respect to respiratory depression. RBP-6000 has been shown to be an efficacious and safe treatment for moderate to severe OUD.

1.3.1 Risk Assessment

The safety profile of buprenorphine is well-established, and the adverse events (AE) expected with buprenorphine are well characterised (see applicable product labelling information). Commonly reported AEs include drug withdrawal syndrome, constipation, headache, nausea and vomiting. Buprenorphine has been approved for multiple indications and routes of administration (e.g., TM, intramuscular, IV, transdermal, rectal and subdermal) in multiple countries and by various manufacturers. Buprenorphine has also been approved as a monthly SC injection for the treatment of OUD.

The systemic safety profile for RBP-6000, given by a healthcare provider in clinical studies, is consistent with the known safety profile of TM buprenorphine with the expected exception of injection site reactions. In the Ph3DB study, participants receiving RBP-6000 300/300 mg (6 doses of 300-mg SC injections), 300/100 mg (300-mg SC injections for the first 2 doses followed by 4 doses of 100-mg SC injections), and placebo (volume-matched ATRIGEL Delivery System SC injections) experienced the following common, non-injection site adverse reactions: constipation, nausea, vomiting, abnormal liver enzymes, headache, sedation and somnolence. Most RBP-6000 injection site reactions were of mild to moderate severity, with 1 report of severe injection site pruritus. None of the injection site reactions were serious. One reaction, an injection site ulcer, led to study treatment discontinuation. The findings reported during post-marketing surveillance are consistent with those observed during the Ph3DB study, and do not indicate any trend of increased safety risk in patients.

In the Ph3DB study, AEs led to premature discontinuation in 4% of the group receiving RBP-6000 compared with 2% in the placebo group.

In the Phase 3 open-label study (RB-US-13-0003, NCT02510014), AEs leading to drug dose reductions were reported in 7.3% of participants receiving RBP-6000. Participants in this long-term study received up to 12 injections of RBP-6000.

In INDV-6000-403 (which used the more rapid induction that is also explored in this current protocol), the most commonly reported treatment-emergent AEs (TEAE) were irritability, anxiety, nausea and pain. The majority of participants reported TEAEs within 48 hours of RBP-6000 administration. Overall, the AE profile and level of sedation indicate that it is safe and tolerable to initiate RBP-6000 following a single dose of TM buprenorphine. There were no unexpected safety findings.

Like the participants in Study INDV-6000-403, participants in the current study will be treatment-seeking but still using opioids, which puts them at high risk for rapid and intense onset of withdrawal symptoms if buprenorphine is administered too soon after their last use of a full opioid agonist. The risk is increased with high doses of potent opioids, such as fentanyl, thus, an on-site dipstick UDS at Screening to identify current

opioids of abuse will support this discussion between the Investigator and study participant. As supported by the results of Study INDV-6000-403, this risk is also mitigated by the requirement for participants to be in withdrawal prior to receiving the first dose of TM buprenorphine. A single dose of 4 mg TM buprenorphine should be sufficient to identify hypersensitivity to buprenorphine and to minimise the occurrence of precipitated withdrawal (as a result of the participant inadequately/incorrectly reporting use of long- or short-acting opioids). Also, use of concomitant medications is permitted to alleviate any withdrawal symptoms that occur, such as ondansetron for nausea/vomiting, clonidine for anxiety/irritability and ibuprofen for pain/body aches, in accordance with SAMHSA TIP 63 2020 guidelines. In addition, following the first injection of 300 mg RBP-6000, TM buprenorphine in increments of 2 to 4 mg up to a maximum dose of 12 mg (inclusive of pre–RBP-6000 TM buprenorphine) may be administered on Day 1 at the discretion of the Investigator to alleviate withdrawal symptoms while on site.

1.3.2 Benefit Assessment

Clear efficacy was demonstrated in the pivotal and additional supporting studies of the RBP-6000 clinical development programme (detailed information provided in the applicable product labelling information). The results of the primary and key secondary efficacy analyses from the Ph3DB study are compelling and are supported by results from other secondary endpoints, as outlined briefly in Section 1.

In addition, a sustained-release formulation of buprenorphine using the ATRIGEL Delivery System offers a number of potential benefits relative to shorter-acting formulations, including improved participant compliance and reduced diversion and misuse, as well as a reduced risk to participants, their families and the community. All participants in this study will receive RBP-6000 (active treatment) and counselling.

Specific to this study, it was observed in the Ph3DB study that the subgroup of injecting opioid users achieved higher percentage abstinence at Week 24 with the 300/300-mg regimen compared with the 300/100-mg regimen and that the difference in the percentage of injecting opioid users remaining abstinent for the last 4 weeks of the 24-week treatment period was higher with 300/300 mg than with 300/100 mg, as detailed in Section 1.2. These observations are consistent with the scientific literature indicating that some individuals require higher buprenorphine exposure and higher levels of mu-opioid receptor occupancy to maximise abstinence and retention in treatment (Hillhouse 2011, Romero-Gonzalez 2017). Thus, participants in the current study (who use opioids via an injection route and/or use high doses of opioids) are expected to benefit from the higher maintenance dose of 300 mg. As demonstrated from the Ph3DB study data, participants who are randomised to the lower maintenance dose of 100 mg will still receive benefit from treatment (in terms of control of withdrawal and craving), even if it is not optimal with respect to abstinence from opioid use.

1.3.3 Overall Risk-Benefit Summary

Taken together, these findings indicate a favourable benefit/risk assessment in the main study to evaluate 2 dose regimens for RBP-6000 for use in patients with OUD who use opioids via an injection route and/or use high doses of opioids, and in the Open-label Induction Sub-study to evaluate rapid induction compared with SoC induction.

2 STUDY OBJECTIVES

2.1 Primary

The primary objective of this study is to compare the efficacy of 100-mg and 300-mg maintenance doses of RBP-6000 administered every 4 weeks in participants who use opioids via an injection route and/or use high doses of opioids.

2.2 Secondary

The secondary objective of this study is to assess the effect of 100-mg and 300-mg maintenance doses of RBP-6000 administered every 4 weeks on treatment retention and parameters of harm reduction (e.g., frequency of opioid use) in participants who use opioids via an injection route and/or use high doses of opioids.

2.3 Exploratory

2.4 Safety

The safety objective of this study is to assess the safety and tolerability of RBP-6000 in participants who use opioids via an injection route and/or use high doses of opioids.

2.5 Sub-Study

Objectives for the Open-label Induction Sub-study are provided in Appendix 22.9.

3 STUDY ENDPOINTS

3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 20 to 38 (inclusive).

3.2 Secondary Efficacy Endpoints

- participants' percentage of days opioids were used out of days assessed (TLFB) over Weeks 10 to 38 (inclusive).

- proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 10 to 38 (inclusive).

- participants' percentage of visits with opioid abstinence (defined as negative UDS and Time-Line Follow Back [TLFB] for opioid use) over Weeks 10 to 38 (inclusive).

- proportion of responders for weekly opioid use, defined as participants' percentage of visits with opioid abstinence being greater than or equal to 80% for the last 5 visits planned for UDS and TLFB assessment over week 30 to week 38.

- proportion of responders for daily opioid use, defined as participants' percentage of days opioids were used out of days assessed (TLFB) being less than or equal to 20% for participants' last 5 visits with observed TLFB post randomisation.

- participants' percentage of visits with opioid abstinence (defined as negative UDS and TLFB for opioid use) overall (Week 2 to 38 inclusive)

- participants' percentage of days opioids were used out of days assessed (TLFB) overall (Week 2 to 38 inclusive)

- for participants who use opioids via the injection route for an average of 5 or more days per week in the last 4 weeks prior to Screening, participants' percentage of days opioids were used via the injection route out of days assessed (TLFB) overall (Weeks 10 to 38 inclusive)

- average number of times opioids were used per week (TLFB) by visit
- change in participants' number of times opioids were used per week from Screening or randomisation baseline to each visit
- proportion of participants abstinent (defined as negative UDS and TLFB for opioid use) by visit
- average number of days opioids were used per week (TLFB) by visit
- treatment retention since randomisation
- proportion of randomised participants who complete the last scheduled injection of RBP-6000

3.3 Exploratory Endpoints

3.4 Safety Assessments

Major safety endpoints include the proportion of participants with at least 1 TEAE of the following types at any time during the treatment period: any TEAE, drug-related TEAE, treatment-emergent serious AE (SAE), drug-related treatment-emergent SAE, or TEAE leading to treatment discontinuation.

Additional safety endpoint assessments include laboratory results, vital signs and use of concomitant medications. Participants will be followed up via telephone the day following Injections 1 and 2 to ask about AEs and associated concomitant medication use.

3.5 Open-label Induction Sub-study Endpoints

Endpoints for the Open-label Induction Sub-study are described in Appendix 22.9.

4 STUDY PLAN

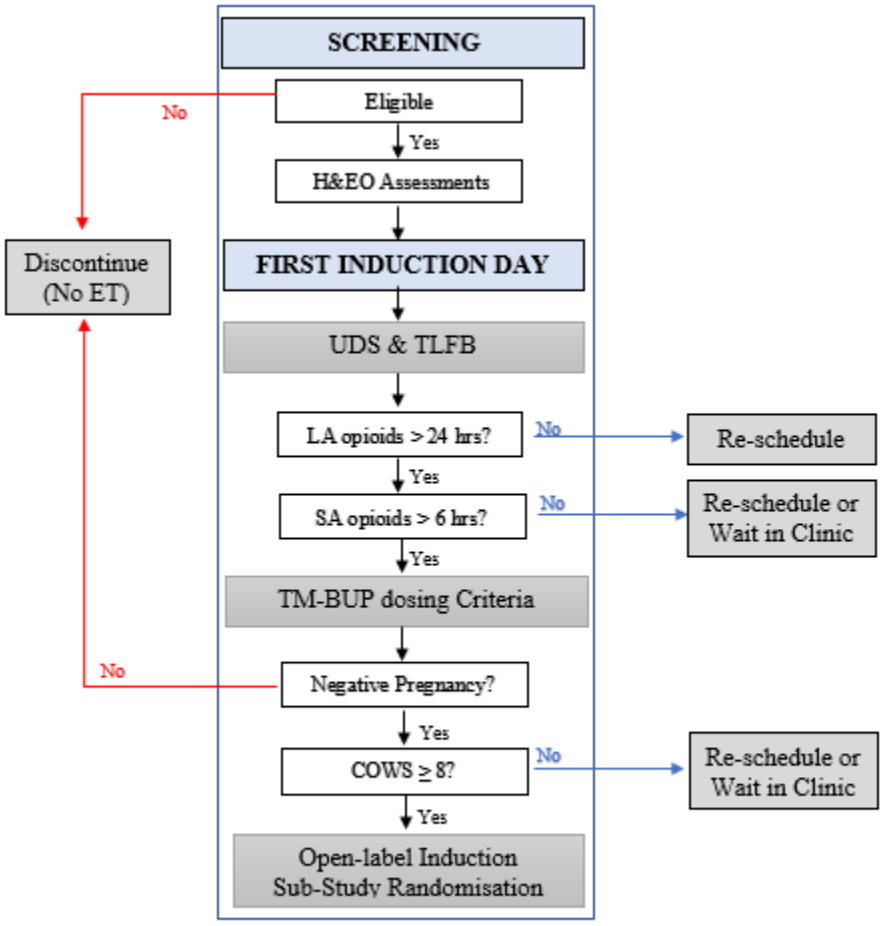
4.1 Study Design

All participants are expected to take part in both the main study and the Open-label Induction Sub-study (i.e., the activities of this nested sub-study are integral to the main study; the objectives and analyses of the sub-study are separate from those in the main study).

4.1.1 Screening and Induction Qualification

This randomised, double-blind, parallel-group, multicentre study will compare the efficacy, safety and tolerability of 100-mg and 300-mg maintenance doses of RBP-6000 administered every 4 weeks to treatment-seeking adult participants with moderate to severe OUD (as assessed by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5]) who use opioids via an injection route and/or use high doses of opioids. The flow of activities from Screening through induction qualification is provided in Figure 2.

Figure 2 Screening Through Induction Qualification Flow Chart



BUP=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; ET=Early Termination; H&EO=Health and Economic Outcomes; LA=Long-acting; SA=Short Acting; TM=transmucosal; UDS=Urine Drug Screen; TLFB=Timeline Follow Back

Participants who provide written informed consent will be assessed for eligibility during an up to 30-day Screening Period. During Screening, the Investigator will ask the participant to self-report recent drug use (including the use of a TLFB) to assess eligibility for high-risk opioid use. Eligibility will be assessed by the participants' TLFB only, and the Investigator may discuss any positive UDS results with the participant only after the completion of the TLFB.

Participants determined to be eligible will be advised to abstain from short-acting opioids (such as morphine sulphate, oxycodone, hydromorphone, oxymorphone or codeine) for at least 6 hours, and long-acting opioids (such as methadone or levorphanol) for 24 hours before arriving at the site for TM buprenorphine induction. Participants will be informed that under-reporting their last use of opioids and undergoing induction with remaining

exposure to opioids places them at high risk for rapid and intense onset of withdrawal symptoms. This risk is increased with high doses of potent opioids, such as fentanyl, which may take longer to clear due to high lipophilicity, redistribution into fat, and prolonged excretion patterns (Mariani 2020). An on-site dipstick UDS at Screening to identify current opioids of abuse will support this discussion between the Investigator and study participant about the optimal period of abstinence for starting induction.

[redacted]

Eligible participants may complete the induction visit once all inclusion and exclusion criteria are confirmed, including applicable laboratory assessments.

Approval from the sponsor must be obtained for any local laboratory and the laboratory normal ranges utilized to determine eligibility for screening. If a local laboratory is utilized for eligibility, the laboratory samples will also be sent to the central laboratory for the baseline analysis value.

If eligibility is confirmed at the screening visit, participants may complete the induction visit. Participants having same-day screening and induction visits are not required to repeat the UDS, pregnancy test, vitals and ECG for the induction visit.

On induction days, eligible participants will provide a urine sample for a UDS dipstick and pregnancy test (female participants of child-bearing potential only). If a female participant has a positive pregnancy test, she will be discontinued and will not proceed with subsequent assessments. The Investigator will ask him/her to self-report recent drug use (including the use of a TLFB assessment). The Investigator may discuss any positive UDS results with the participant only after completion of the TLFB:

1. Participants who report that they have used long-acting opioids within the previous 24 hours will not be permitted to proceed with induction until the 24-hour period has passed. If necessary, induction may be rescheduled. The 1st day of the repeat induction should be scheduled within 30 days of informed consent.

2. Participants who have used short-acting opioids within the previous 6 hours may be permitted to proceed with the induction visit at the discretion of the Investigator.

All concomitant medications used since Screening will be reviewed.

The COWS will then be completed to assess withdrawal symptoms.

Participants must meet **both** of the following criteria to receive TM buprenorphine:

1. Have a negative pregnancy test (if female and of childbearing potential)
2. Be in withdrawal (COWS score ≥8)

If a participant's COWS score is <8, the participant may either be re-scheduled for induction within 30 days of informed consent or remain at the site (at the Investigator's discretion), and the COWS may be repeated until the participant has a score ≥8. Only when the COWS score is ≥8 and all pre-TM buprenorphine assessments have been completed may the participant receive TM buprenorphine to begin induction.

4.1.2 Induction

When the participant has met the TM buprenorphine dosing criteria, he/she will be randomised at a 2:1 ratio to 1 of 2 induction arms: RBP-6000 rapid induction or SoC induction. Due to the potential for fentanyl use to impact the response to TM buprenorphine induction, randomisation will be stratified according to the same-day UDS result for fentanyl (negative or positive).

The following points apply to both induction arms:

- After randomisation, the participant will complete the pre-TM buprenorphine assessments: [redacted] vital signs, 12-lead electrocardiogram (ECG) and a review of AEs.
- If the participant displays any allergic/hypersensitivity reaction to TM buprenorphine, the participant will be discontinued from the study.
- Participants experiencing precipitated withdrawal symptoms post-TM buprenorphine may be treated symptomatically (see Section 9.13).

4.1.2.1 Rapid Induction

The flow of activities for participants in the rapid induction arm is provided in Figure 3.

After completing the pre-TM buprenorphine assessments, participants will then be administered 4 mg of TM buprenorphine.

After a minimum of 1 hour has elapsed since the 4-mg dose of TM buprenorphine was administered, the participant will be re-assessed for withdrawal symptoms (COWS) and tolerability (AEs). Participants must meet **all** of the following criteria to receive RBP-6000 using rapid induction:

1. The participant does not display any allergic/hypersensitivity reaction to TM buprenorphine.

2. Based on the Investigator's judgment, the participant did not experience precipitated withdrawal symptoms from the most recent TM buprenorphine administration that would prevent RBP-6000 administration.

3. Based on the Investigator's judgment, the participant is not sedated (i.e., participant cannot be easily aroused by external stimuli).

After receiving TM buprenorphine, if the participant is sedated or has precipitated withdrawal symptoms that would prevent RBP-6000 administration, in the opinion of the Investigator, the participant may either remain in the clinic to repeat the 4 mg TM buprenorphine later that same day or may return to the site and repeat the induction within 30 days of informed consent.

If the participant is eligible for dosing with RBP-6000, pre–RBP-6000 assessments will be conducted including, but not limited to, vital signs, [redacted] will be collected. If the participant is eligible, 300 mg RBP-6000 may be administered SC and the visit will be considered Day 1.

Participants will be asked to remain in the clinic for at least 4 hours post-RBP-6000. A COWS assessment will be completed at 1, 2 and 4 hours and an injection site evaluation will be completed at 1 and 2 hours post–RBP-6000. [redacted] All AEs and concomitant medications should be recorded. If the participant experiences withdrawal symptoms post RBP-6000 on Day 1, the participant may be treated symptomatically (SAMHSA TIP 63 2020; see Section 9.13 for treatment of withdrawal symptoms). Also, following the first injection of 300 mg RBP 6000, TM buprenorphine in increments of 2 to 4 mg up to a maximum dose of 12 mg (inclusive of pre–RBP-6000 TM buprenorphine) may be administered on Day 1 at the discretion of the Investigator to alleviate withdrawal symptoms while on site.

Prior to the participant leaving the site, the Investigator will be asked to assess the following:

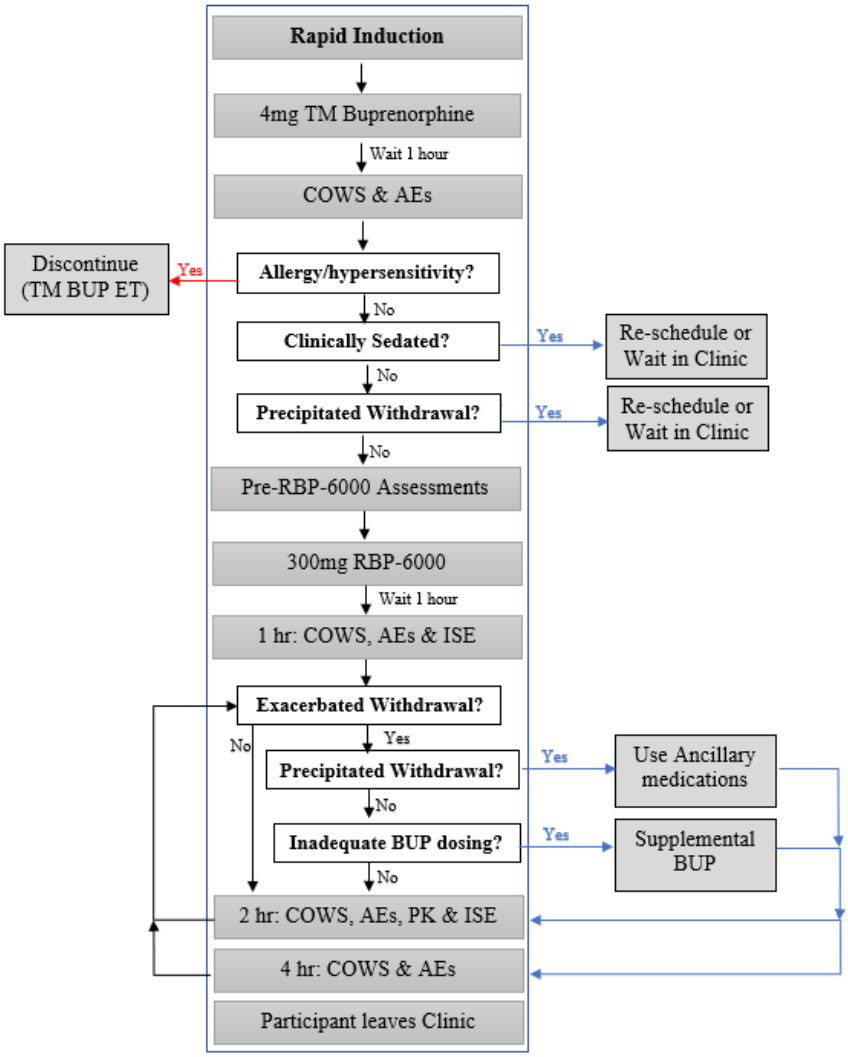
- Did the participant experience precipitated withdrawal after TM buprenorphine, and if so, which AEs were associated with the event?

- Did the participant experience precipitated withdrawal after the RBP-6000 injection and if so, which AEs were associated with the event?

- After how many hours would you have let the participant leave the clinic if you had not been required to observe them for at least 4 hours post injection?

The participant will be followed up via telephone the day after the first RBP-6000 injection.

Figure 3 Rapid Induction Flow Chart



AEs=Adverse Events; BUP=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; ET=Early Termination; ISE=Injection Site Evaluation; PK=pharmacokinetic; TM=transmucosal;

4.1.2.2 Standard of Care (SoC) Induction

After completing the pre-TM buprenorphine assessments, participants should then be inducted per SoC according to the applicable TM buprenorphine product labelling

information, that is, a participant should be dose-adjusted onto TM buprenorphine for a minimum of 7 days.

On the first induction day, participants will be asked to remain in the clinic for at least 5 hours after the first TM buprenorphine dose, completing COWS assessments at 1, 2, 3 and 5 hours post TM buprenorphine. All AEs and concomitant medications should be recorded. If the participant experiences exacerbated withdrawal symptoms at any time, he/she may be treated symptomatically.

Prior to the participant leaving the site, the Investigator will be asked to assess the following:

- Did the participant experience precipitated withdrawal after TM buprenorphine, and if so, which AEs were associated with the event?

Any doses of TM buprenorphine administered at the site, dispensed to the participant and taken by the participant outside of the clinic should be recorded. For reconciliation, participants will be asked to return any doses not taken as well as the empty packaging for all doses taken. The Investigator may ask the participant to return for dose adjustment as many times as necessary per SoC, recording any AEs and concomitant medications at each visit.

Participants must meet **all** of the following criteria to receive RBP-6000 using SoC induction:

1. The participant has been dose-adjusted onto TM buprenorphine for a minimum of 7 days and, based on the Investigator's judgment, appears eligible for dosing with RBP-6000.

2. The participant does not display any allergic/hypersensitivity reaction to TM buprenorphine.

3. Based on the Investigator's judgment, the participant did not experience precipitated withdrawal from the most recent TM buprenorphine administration that would prevent RBP-6000 administration.

4. Based on the Investigator's judgment, the participant is not sedated (i.e., participant cannot be easily aroused by external stimuli).

5. The participant has a negative pregnancy test (if female and of childbearing potential).

If a female participant has a positive pregnancy test, she will be discontinued from the study and will not proceed with subsequent assessments.

When the Investigator confirms eligibility for dosing with RBP-6000, pre–RBP-6000 assessments will be conducted including (but not limited to) TLFB, COWS, [redacted] 12-lead ECG, vital signs, [redacted] will be collected. If the participant is eligible, 300 mg RBP-6000 may be administered SC and the visit will be considered Day 1. Following the first injection of RBP-6000, the participant will remain at the site for at least 4 hours after the injection and be monitored for safety and tolerability. A COWS assessment will be completed at 1, 2 and 4 hours and an injection site evaluation will be completed at 1 and 2 hours post–RBP-6000. [redacted] All AEs and concomitant medications should be recorded.

Prior to the participant leaving the site, the Investigator will be asked to assess the following:

- Did the participant experience precipitated withdrawal after the RBP-6000 injection and if so, which AEs were associated with the event?
- After how many hours would you have let the participant leave the clinic if you had not been required to observe them for at least 4 hours post injection?

The participant will be followed up via telephone the day after the first RBP-6000 injection.

4.1.3 Second Dose of RBP-6000

The second RBP-6000 dose will be administered at Week 2, 1 week (+4 days) after the first injection.

Participants will be followed up via telephone the day after the second RBP-6000 injections.

4.1.4 Double-blind Treatment Period

Participants will be randomised at Week 6 prior to Injection 3 in a 1:1 ratio to receive maintenance doses of either 300 mg or 100 mg every 4 weeks (-2/+4 days) for up to a total of 8 maintenance injections. Randomisation prior to the third RBP-6000 dose will be stratified according to opioid use predominantly via injection route at Screening (yes or no) and Week 6 UDS result for opioids (negative or positive). Opioid use predominantly via injection route at Screening is defined as using opioids via the injection route for an average of 5 or more days per week in the last 4 weeks at Screening (i.e., meeting Inclusion Criterion 5a).

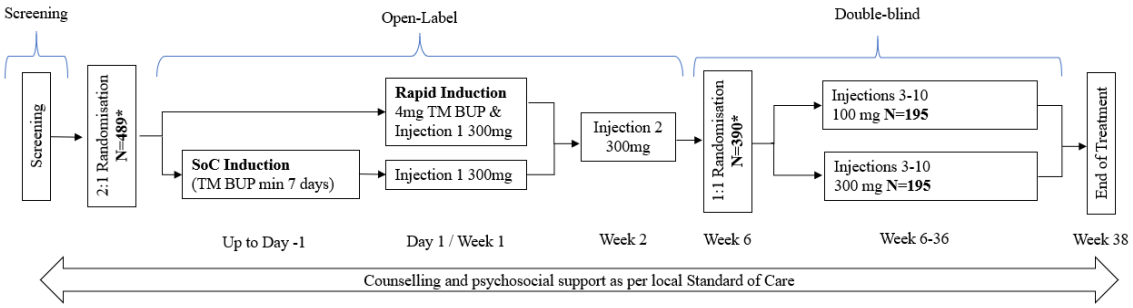
Participants will return to the site for weekly UDS and collection of self-reported drug use, including TLFB, from Weeks 1 to 10. From the fourth injection until the end of the treatment period (Weeks 10 to 38), UDS and self-reported drug use (including TLFB) will be obtained at every injection visit. In addition, random visits (2 weeks post each injection ±7 days) are to be scheduled by the Investigator to complete UDS and TLFB only. All participants will receive counselling, per SoC, from the first induction day through the end of the treatment period (Week 38/EOT).

All participants will continue study treatment until they complete the EOT visit (Week 38). Participants who prematurely discontinue RBP-6000 treatment will complete the early termination (ET) visit. During the last injection visit (Week 34) through the EOT visit (or the ET for those who prematurely discontinue), the Investigator or a medically qualified sub-Investigator will discuss available treatment options for continued treatment. Any participant with ongoing AEs at the EOT or ET visit will also be followed up by phone 2 weeks later for the End of Study (EOS) visit to assess any ongoing AEs and concomitant medications associated with those ongoing AEs only.

Participants are not permitted to use supplemental TM buprenorphine after they leave the site on Day 1. No dose increases or decreases of RBP-6000 are allowed.

If the participant experiences withdrawal symptoms at any time, he/she may be treated symptomatically (SAMHSA TIP 63 2020; see Section 9.13 for treatment of withdrawal symptoms).

4.2 Study Schematic



BUP=buprenorphine; min=minimum; SoC=standard of care; TM=transmucosal

5 POPULATION

5.1 Number of Participants

It is planned for approximately 390 participants to be randomised immediately prior to their third injection, 4 weeks after their second 300-mg dose of RBP-6000, at a 1:1 ratio (195 per group) to receive either 300 mg RBP-6000 or 100 mg RBP-6000 for subsequent monthly doses. [redacted]

5.2 Inclusion Criteria

A participant must meet **all** of the following criteria to be eligible for inclusion in this study:

1. Has signed the informed consent form (ICF) and is able and willing to comply with the requirements and restrictions listed therein.

2. Is 18 years of age or older at the time of signing the ICF.

3. Currently meets DSM-5 criteria for moderate or severe OUD.

4. Has a history of OUD as defined by documented medical history of OUD for at least 90 days immediately prior to providing informed consent.

5. Meets at least 1 of these criteria for high-risk opioid use at the Screening visit:

    a. using opioids via the injection route for an average of 5 or more days per week in the last 4 weeks.

    b. using at least 500 mg IV heroin equivalent (e.g., 1250 mg IV morphine) or self-reported use of any dose of highly potent synthetic opioids (fentanyl and analogues excluding transdermal patches) for an average of 5 or more days per week in the last 4 weeks by any route (See Appendix 22.8, Morphine Dose Analgesic Equivalence Table).

6. Is seeking medication for the treatment of OUD.

7. Is an appropriate candidate for opioid partial-agonist MOUD in the opinion of the Investigator or medically qualified sub-Investigator.

8. Agrees not to use buprenorphine-containing products other than those administered as part of study treatment for the duration of the treatment period.

9. A female participant is eligible to participate if she is not pregnant (as confirmed by a negative serum or urine human chorionic gonadotrophin test, not lactating and, if of childbearing potential, agrees not to become pregnant while on the study and to use medically acceptable means of contraception while on the study). The following methods of contraception are considered to be medically acceptable: established use of oral, injected or implanted hormonal contraception; placement of an intrauterine device or intrauterine system; or use of a double-barrier method of contraception (condom or occlusive cap with use of a spermicide).

5.3 Exclusion Criteria

A participant will not be eligible for inclusion in this study if **any** of the following criteria apply:

1. Has current diagnosis, other than OUD, requiring chronic opioid treatment.

2. Has concurrent primary substance use disorder, as defined by DSM-5 criteria, other than opioid, tobacco, cannabis or alcohol use disorders.

3. Meets DSM-5 criteria for severe alcohol use disorder.

4. Has had significant traumatic injury or major surgical procedure (as defined by the Investigator) within 30 days prior to the first dose of RBP-6000 or still recovering from prior such injury or surgery.

5. Has congenital long QT syndrome, history of prolonged QT in the 3 months prior to Screening, or history of medications or other factors that are at risk for Torsades de Pointes.

6. Has abdominal area unsuitable for SC injections (e.g., nodules, scarring, lesions, excessive pigment).

7. Has history of suicidal ideation within 30 days prior to informed consent or history of a suicide attempt in the 6 months prior to informed consent.

8. Has uncontrolled intercurrent illness including, but not limited to, a medical or psychiatric illness/social situation that would limit compliance with study requirements or compromise the ability of the participant to provide written informed consent.

9. Has any other active medical condition, organ disease or concurrent medication or treatment that may either compromise participant safety or interfere with study endpoints.

10. Has total bilirubin ≥1.5 × upper limit of normal (ULN) (with direct bilirubin >1.3 mg/dL), ALT ≥3 × ULN, AST ≥3 × ULN, serum creatinine >2 × ULN, or international normalised ratio (INR) >1.5 × ULN at Screening.

11. Has known allergy or hypersensitivity to buprenorphine or any component of the ATRIGEL Delivery System.

12. Is undergoing concurrent or has had prior treatment with any long -acting form of a buprenorphine-containing product in the past 2 years, or if >2 years has a positive UDS for buprenorphine at screening; treatment with oral buprenorphine, oral naltrexone or methadone products within 14 days prior to consent; or treatment with depot naltrexone within the 3 months prior to consent.

13. Is undergoing concurrent treatment with another investigational agent or enrolment in another clinical study (except for an observational study) or treatment with another investigational agent within 30 days prior to Screening.

14. Is undergoing concurrent treatment with medications contraindicated for use with buprenorphine as per local prescribing information.

15. Has any pending legal status or pending legal action that could prohibit full participation in or compliance with study procedures.

16. Is under court order requiring treatment for OUD.

17. Is a member of site staff and/or has a financial interest in Indivior, or is an immediate family member of either the site staff and/or Indivior employee, directly involved in the study.

5.4 Eligibility Criteria for Open-label Induction Sub-study

Inclusion and exclusion criteria for participants in the Open-label Induction Sub-study are identical to those in the main study.

5.5 Participant Screening

Participants who provide written informed consent will be assessed for eligibility during an up to 30-day Screening Period.

Participants determined to be eligible will be advised to abstain from short-acting opioids (such as morphine sulphate, oxycodone, hydromorphone, oxymorphone or codeine) for at least 6 hours, and long-acting opioids (such as methadone or levorphanol) for at least 24 hours before arriving at the site for TM buprenorphine induction. It will be explained that under-reporting the last use of opioids puts the participant at high risk for rapid and intense onset of withdrawal symptoms.

5.6 TM Buprenorphine Dosing Criteria

Dosing criteria for the induction are provided in Section 4.1.1.

5.7 RBP-6000 Dosing Criteria

Dosing criteria for the first RBP-6000 injection are provided in Section 4.1.2.1 (rapid induction) and Section 4.1.2.2 (SoC induction).

5.8 Deviation from Inclusion/Exclusion Criteria

Waivers from inclusion and exclusion criteria are not allowed because they have the potential to jeopardise participant safety, the scientific integrity of the study or regulatory acceptability of the data. Indivior does not grant waivers to the protocol-defined inclusion and exclusion criteria, and strict adherence to these criteria as outlined in the protocol is essential.

5.9 Participant Rescreening

Participants not meeting one or more inclusion/ exclusion criteria will be screen failures. Participants who have a change in clinical status may be rescreened with documented approval of the Sponsor's Medical Monitor.

Eligible participants who were not randomized to an induction arm (Section 4.1.2) within the 30-day screening period, may be rescreened for study participation following documented approval of the Medical Monitor.

Eligible participants who were randomized to an induction arm (Section 4.1.2), may not be rescreened, regardless of whether they were administered TM buprenorphine.

If a participant is rescreened, all screening assessments, as described in Appendix 22.1, will be repeated, including the re-signing of informed consent. The 30-day screening window will begin upon signature of the informed consent.

6 STUDY CONDUCT

6.1 Screening Period

The Screening period begins once written informed consent is obtained and ends at administration of TM buprenorphine.

6.1.1 Participant Screening

Participants are considered screened once written informed consent is obtained; a participant identification number is then assigned. The participant identification number will be used to identify the participant during the Screening process and throughout study participation.

The Investigator is responsible for maintaining a master list (i.e., a participant identification list) of all consented participants and will document all participants that did not meet study eligibility criteria (i.e., screen failures), including reason(s) for ineligibility (i.e., a participant Screening and Enrolment Log). This document will be reviewed by Indivior or designated representative for accuracy and completeness. Ineligible participants, as defined by the protocol-specific inclusion and exclusion criteria, should not receive study drugs (TM buprenorphine or RBP-6000) and should be documented as screen failures.

6.1.2 Not Enrolled (Discontinuation Prior to Enrolment)

A participant will be considered discontinued prior to enrolment if written informed consent is obtained but the participant does not receive TM buprenorphine. Participants who discontinue from the study before TM buprenorphine administration will not be required to complete an EOT visit. Reasons for discontinuation prior to enrolment (e.g., withdrawal of consent, does/not meet specified inclusion or exclusion criteria, or does not meet TM buprenorphine dosing criteria) will be recorded in the electronic case report form (eCRF).

6.2 Enrolment

A participant will be considered enrolled if he/she receives at least 1 dose of TM buprenorphine, as defined in the study procedures.

6.3 TM Buprenorphine Induction Period

The TM Buprenorphine Induction Period begins when the participant receives TM buprenorphine and ends at the first RBP-6000 administration.

6.4 TM Buprenorphine Early Termination

Participants who discontinue from the study after TM buprenorphine administration and before any RBP-6000 administration will be withdrawn from the study. Any participants with ongoing AEs will be contacted via telephone 24 to 72 hours after TM buprenorphine administration to follow up on those ongoing AEs and associated concomitant medications.

6.5 Treatment Period

The treatment period begins when the participant receives TM buprenorphine and ends when the Week 38 EOT visit or ET visit has been completed.

6.5.1 Open-label Treatment Period

The Open-label Treatment Period (OLTP) begins when the first TM buprenorphine dose is given and ends immediately prior to a participant receiving double-blind RBP-6000 Injection 3. Note that pre-dose assessments for Injection 3 are considered part of the OLTP.

6.5.2 Randomisation and Double-Blind Treatment Period

The randomised Double-blind Treatment Period (DBTP) begins when the participant receives randomised treatment at Week 6 (Injection 3) and ends when the Week 38 EOT visit or ET visit has been completed.

6.6 Participant Completion

A completed participant for the main study is one who has completed the study through the EOT visit (Week 38).

A completed participant for the Open-label Induction Sub-study is one who has been enrolled and has completed Injection 3, otherwise he/she is considered prematurely discontinued. Note that participants who prematurely discontinue from the Open-label Induction Sub-study will also prematurely discontinue from the main study.

6.7 Premature Discontinuation

6.7.1 Participant Withdrawal from Treatment

[redacted]

6.7.2 Participant Withdrawal from the Study

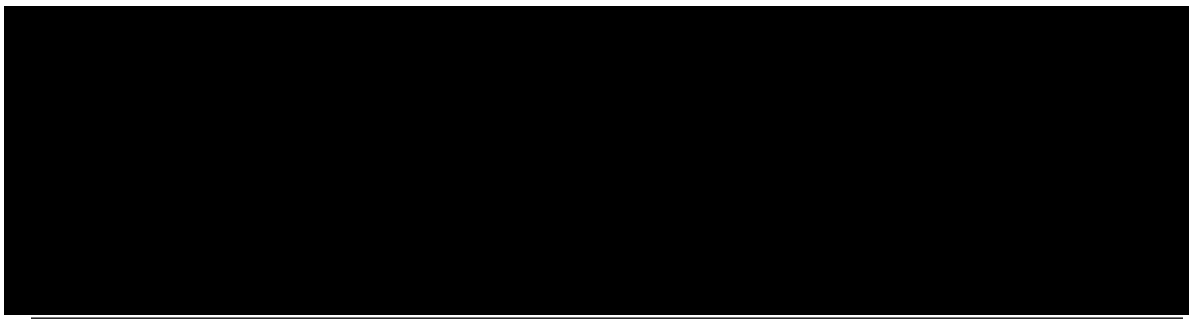
If the participant has permanently discontinued study treatment and is no longer being followed for study assessments and procedures (including follow-up procedures), he/she will be considered withdrawn from the study. The primary reason for withdrawing from the study must be entered into the eCRF (e.g., participant is lost to follow-up, Indivior terminates the study, or Investigator discretion).

Participants who discontinue from the study before TM buprenorphine administration will not be required to have any follow up.

Participants who discontinue from the study after TM buprenorphine administration, and before RBP-6000 administration and have ongoing AEs, will be contacted via telephone 24 to 72 hours after TM buprenorphine administration to assess those ongoing AEs and associated concomitant medications.

All participants who receive RBP-6000 (including those who wish to discontinue early), will be encouraged to attend the ET visit 4 weeks after the last RBP-6000 administration. If the participant has any ongoing AEs, he/she will be contacted via telephone 2 weeks later to assess those ongoing AEs and associated concomitant medications.

6.7.3 Liver Chemistry Stopping Criteria



6.7.4 QTc Stopping Criteria

6.7.5 Participant Withdrawal of Consent

If a participant withdraws consent, he/she will not receive any additional doses of study treatment. However, the participant may be offered additional tests as needed to monitor safety (e.g., EOT safety assessments or procedures).

6.7.6 Participants Lost to Follow-up

In cases of a missed visit, the Investigator or designee must attempt to contact the participant and re-schedule as soon as possible. The Investigator or designee must counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

In the event a participant is lost to follow-up, the Investigator or designee must make a reasonable effort to contact the participant. Two documented attempts (e.g., phone, email, etc.) to contact the participant followed by a certified mailed letter is considered reasonable.

For the purpose of documenting date of discontinuation for a participant confirmed to be lost to follow-up, the date of discontinuation should be the date of last contact with the participant.

- In the case where a certified letter is sent but not confirmed as received by the participant, the date of discontinuation is the date of the participant's last study visit.

- In the case where a certified letter is sent and has been confirmed as received by the participant, the date of discontinuation is the date of the confirmed participant receipt.

In the event that neither of these above cases applies (which should be explained in the source documents), the date of discontinuation is the date of the participant's last study visit.

7 STUDY SUSPENSION OR TERMINATION

Indivior reserves the right to temporarily suspend and/or permanently discontinue the study at any time and for any reason, including safety or ethical concerns or severe non-compliance. If such action is taken, Indivior will discuss the rationale for the decision with the Investigator. In cases where a study is suspended or terminated for safety reasons, Indivior will promptly inform Investigators and the Regulatory Authorities of this action and the reason(s) for the suspension or termination.

If required by applicable regulations, the Investigator must inform the Institutional Review Board/Independent Ethics Committee (IRB/IEC) promptly and provide the reason(s) for the suspension or termination. If the study is prematurely discontinued, all study data and study drug remaining on site must be returned to Indivior or its designated representative.

8 DESCRIPTION OF STUDY PROCEDURES

Study assessments and procedures, including the timing of assessments, are summarised in tables accessible through Table 2. [redacted]

A signed written ICF must be obtained from the participant before any study assessments or procedures may be performed. At Screening, if an assessment or procedure has already been performed as part of routine SoC and was completed within the protocol-specific Screening window, the assessment or procedure does not need to be repeated, unless clinically indicated and must be clearly documented in the source that the assessment was performed as part of SoC. All assessments and procedures may be performed more frequently, if clinically indicated, and will be recorded in the eCRF as unscheduled visits.

8.1 Demographics and Medical/Psychiatric History

A detailed medical and psychiatric history will be obtained during the Screening Period. This will include information regarding the participant's complete history of relevant medical and psychiatric conditions, diagnoses, procedures, treatments, medications, demographics (including sex, race, age and ethnicity), and use of alcohol, tobacco and caffeine. Eligible participants must have a documented history of moderate or severe OUD as defined by DSM-5, and must be seeking medication for treatment of OUD. Any updates to medical or psychiatric history information made available during the study will be captured.

8.2 Substance Use History

A detailed alcohol and drug use history will be obtained during the Screening Period. This will include information regarding the participant's complete history of drug use (e.g., opioids, barbiturates, benzodiazepines, amphetamines/methamphetamine and phencyclidine), any detox or maintenance treatment for OUD, and any overdose history.

8.3 Efficacy Assessments

Details on how to complete TLFB [redacted] will be provided to the site.

8.3.1 Urine Drug Screening

Dipstick and centrally tested UDS will include substances listed in Table 1. A urine dipstick will be performed on-site at Screening, first TM buprenorphine induction day/Day 1 and Week 6. All other UDS will be tested centrally. Additional unscheduled

UDS (dipstick) may be performed as determined by the Investigator or a medically qualified sub-Investigator as per standard-of-care and/or if abuse is suspected.

Additional information related to the collection and handling of urine specimens is located in the laboratory manual.

8.3.2 TimeLine Follow Back

The TLFB Interview is a reliable and validated method administered by an interviewer to assess recent drug use in adults (Fals-Stewart 2000). The interview instrument asks participants to retrospectively estimate their daily drug use for each of the past 7 days prior to the visit. The TLFB captures only which days drugs were used ("used" or "did not use") by specific opioid drug, or by drug class for other substances (see below). Therefore, additional self-report questions for opioids capturing the main route of use (and more specifically, if an injectable route was used) and the number of times used each day will also be added to those answered "used".

The interview will take approximately 10 to 30 minutes to complete.

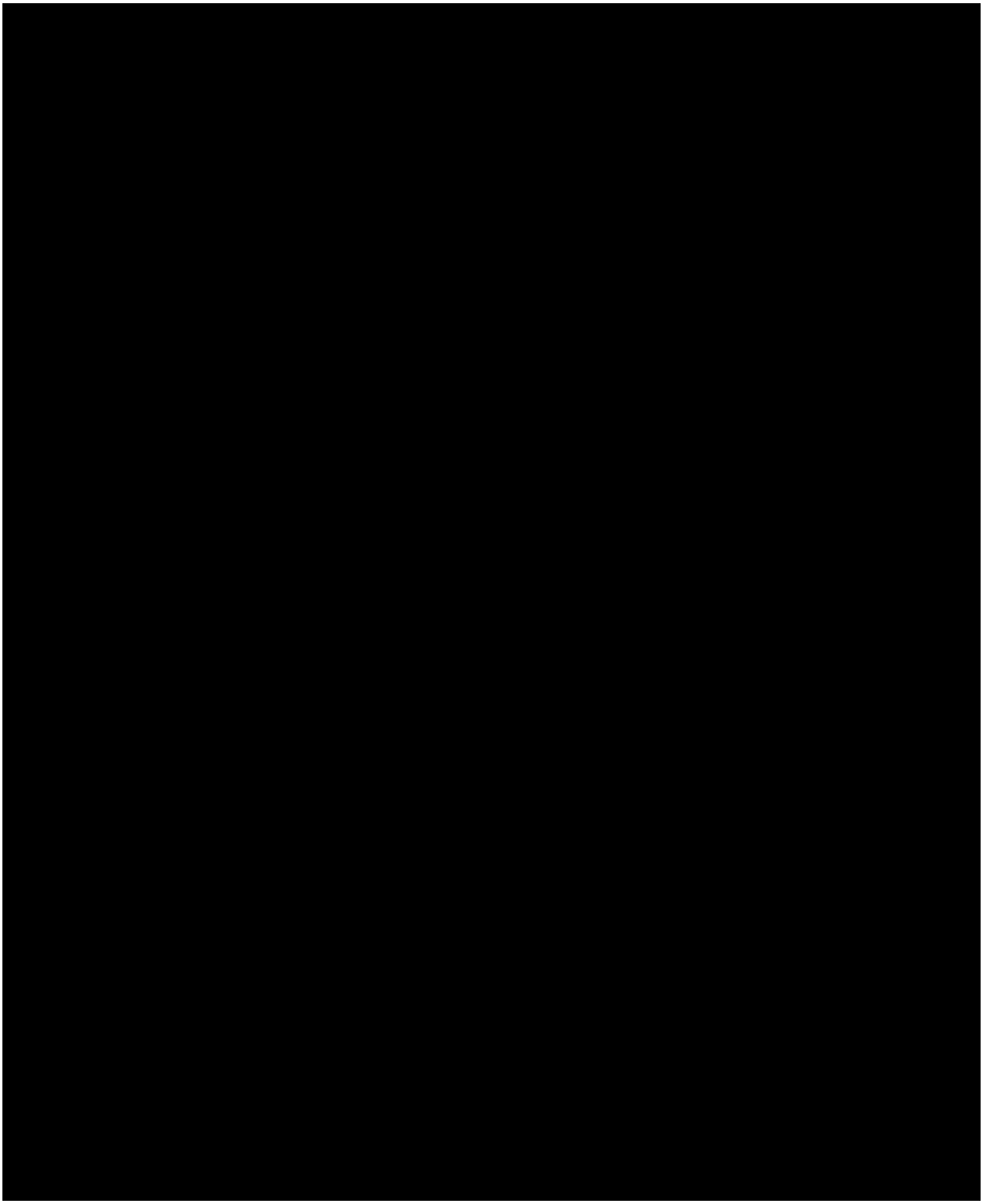
Drugs to be assessed in this study include opioids, oxycodone, fentanyl, morphine, methadone, buprenorphine, cocaine, cannabinoids, barbiturates, benzodiazepines, amphetamines/methamphetamine and phencyclidine. The TLFB is administered and scored electronically.

8.3.4 Clinical Opiate Withdrawal Scale

The COWS is an 11-item, validated instrument used to assess symptoms of opiate withdrawal (Tompkins 2009, Wesson 2003). The score is the sum of the response to each of the 11 items and ranges from 0 to 48. A score of 5 to 12 is considered mild, 13 to 24 is moderate, 25 to 36 is moderately severe, and a score >36 is considered severe withdrawal.

Where feasible, each participant should be assessed by the same qualified and trained individual throughout the course of the study. The COWS is administered and scored electronically.

On all injection days, the COWS will be completed prior to RBP-6000 injection; the COWS will also be completed post injection on Day 1 (i.e., after the first injection of RBP-6000).



8.7 Safety Assessments

Definitions and procedures for reporting AEs and SAEs are provided in Section 10 and Section 11, respectively.

8.7.1 Physical Examination

A complete physical examination will be conducted by the Investigator or a medically qualified sub-Investigator as noted on the Schedules of Events displayed in Table 2. This examination will include an assessment of general appearance, skin and extremities, head and neck, lymph nodes, eyes, ears, nose, throat, thyroid, neurological system, lungs, cardiovascular system, and abdomen (liver and spleen). The examination will not include a breast, pelvic or rectal exam, unless clinically indicated.

Weight (kg) will be assessed as shown in the Schedules of Events displayed in Table 2. Height (cm) will be recorded at Screening only.

8.7.2 Injection site Evaluations

The RBP-6000 injection site will be evaluated for signs of attempted depot removal. Any removals will be reported as an AE of special interest as directed in Section 10.1. If there is any evidence of attempted depot removal present, the Investigator must discuss with the medical monitor about whether the participant should remain in the study. Any injection-site reactions or infections will be recorded as AEs. Injection-site evaluations will be performed according to the schedule of assessments, per Table 2.

8.7.3 Clinical Laboratory Tests

Clinical laboratory tests will be performed in a licensed clinical laboratory. Urine pregnancy tests may be performed using a dipstick test. Participants are to be in a sitting/supine position during blood collection. The following clinical laboratory tests (Table 1) will be performed according to the Schedules of Events displayed in Table 2.

Table 1 List of Laboratory Tests

Haematology:
Haematocrit
Haemoglobin
Mean corpuscular haemoglobin
Mean corpuscular haemoglobin concentration
Mean corpuscular volume
Platelet count
Red blood cell (RBC) count
White blood cell (WBC) count with 5-part differential

Urinalysis:
Appearance
Bilirubin
Colour
Glucose
Ketones
Leucocyte esterase
Microscopic examination of sediment[a]
Nitrite
Occult blood
pH
Protein
Specific gravity
Urobilinogen

Other:[b]
HIV-1 and -2 antibodies
Hep C and Hep B antibodies

Serum Chemistry[c]:
Albumin
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)
Amylase
Aspartate aminotransferase (AST)
Blood urea nitrogen
Calcium
Calculated creatinine clearance
Carbon dioxide
Chloride
Creatinine
Creatine kinase
(subtypes may be performed if required for clinical management)
Gamma-glutamyl transferase
Glucose (non-fasting)
Lactate dehydrogenase
Lipase
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total is high)
Total protein

Coagulation:
PTT
PT with INR

Pregnancy:
Urine pregnancy (only for females not postmenopausal or surgically sterile for at least 1 year)
Serum Pregnancy

Urine Drug Screen (UDS):
Opioids
Oxycodone
Fentanyl
Morphine
Methadone
Cocaine
Amphetamines
Methamphetamine
Ecstasy
Cannabinoids
Barbiturates
Benzodiazepines
Phencyclidine
Buprenorphine (results collected in CRF from on-site dipstick at screening and first induction day only)

Hep=hepatitis; HIV=human immunodeficiency virus; INR=international normalised ratio; PT=prothrombin time; PTT=partial thromboplastin time

[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] The HIV-1/HIV-2, Hep B and Hep C antibody testing to be performed at Screening only in the absence of a positive (documented) medical history for these conditions and at EOT/ET only if negative at Screening.

[c] The tests listed in serum chemistry are a minimum required list. Additional tests may be performed if included in the laboratory panel.

8.7.3.1 Sample Collection, Storage, and Shipping

Details for the collection, preparation, storage and shipment of laboratory specimens is outlined in the laboratory manual(s).

8.7.3.2 Laboratory Result Review

The Investigator or a medically qualified sub-Investigator will review the laboratory results and clearly identify those that are "abnormal, not clinically significant" as well as those that are "abnormal, clinically significant". Any abnormal clinically significant laboratory value will be reported as an AE in the eCRF. The Investigator or a medically qualified sub-Investigator will sign and date laboratory reports as evidence of review.

8.7.4 Vital Signs

Evaluation of vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature) will occur after the participant has been sitting for ≥3 minutes. Any clinically significant vital sign measurement (as determined by the Investigator or a medically qualified sub-Investigator) will be recorded as an AE and re-assessed at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.

On injection days, the vital signs will be completed prior to RBP-6000 injection.

8.7.5 12-Lead Electrocardiograms

Electrocardiograms should be collected on the same model ECG machine for each participant, where feasible. All ECGs will be performed after the participant has been in a supine position for ≥5 minutes and before collecting any blood samples at that visit. Recordings will be taken using an ECG machine that automatically calculates the heart rate and measures QT and QTc intervals and can perform an arrhythmia analysis. The ECGs will be read locally.

On injection days, the 12-lead ECG will be completed ≤60 minutes prior to RBP-6000 injection.

Additional 12-lead ECGs may be performed at the discretion of the Investigator or medically qualified sub-Investigator. The findings of the ECGs will be marked by the Investigator or medically qualified sub-Investigator as normal, abnormal – not clinically significant, or abnormal – clinically significant. All ECGs that are considered abnormal – clinically significant should be evaluated for a change from baseline and must be captured as an AE.

8.8 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or ICH/GCP requirements. The noncompliance may be on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly and in accordance with ICH E6. It is the responsibility of the Investigator and study site staff to use continuous vigilance to identify and report deviations to Indivior or specified designee and the IRB/IEC. All deviations must be addressed in the study source documents. Protocol deviations must be sent to the local IRB/IEC as required. The Investigator and study site staff are responsible for knowing and adhering to the IRB/IEC's requirements.

9 STUDY DRUG MANAGEMENT

The term "study drug" is used throughout the protocol to describe the TM buprenorphine and/or RBP-6000 received by the participant as per the protocol design. Study drug may therefore refer to TM buprenorphine and/or RBP-6000.

The term "study treatment" refers to the participants receiving the study drugs per protocol in combination with counselling.

Transmucosal buprenorphine will be administered per the applicable product labelling information at the timepoints defined in this protocol. The site will source commercially available TM buprenorphine for the study; RBP-6000 will be provided by the Sponsor.

For this reason, only RBP-6000 is covered in the following section.

9.1 Description

9.1.1 Formulation

RBP-6000 is a colourless to amber sterile solution for SC injection designed to deliver buprenorphine at a dose of 100 mg or 300 mg at a controlled rate over a 1-month (4-week) period. The active ingredient in RBP-6000 is buprenorphine (free base), a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist. Buprenorphine is dissolved in the ATRIGEL Delivery System at 18% by weight and is a biodegradable 50:50 poly(DL-lactide-co-glycolide) polymer and a biocompatible solvent, N-methyl-2-pyrrolidone. Refer to the applicable product label for additional information on the physical and chemical properties of the drug substance and for a list of excipients.

Adequate precautions must be taken to avoid direct contact with the study drug. Occupational hazards and recommended handling procedures are provided in the Safety Data Sheet.

9.1.2 Storage

RBP-6000 must be stored in the refrigerator at 2° to 8°C (35.6° to 46.4°F) in a secure location with limited access.

Once outside the refrigerator, RBP-6000 may be stored in its unopened original packaging at room temperature, 15°C to 30°C (59°F to 86°F), for up to 7 days prior to administration. Discard RBP-6000 if left at room temperature for longer than 7 days.

A product unit removed from refrigeration that has been exposed to room temperature (no more than 30°C) for no more than 24 hours while still in the original unopened

packaging, can be returned to refrigerated storage 1 time only and upon subsequent removal may still be held at up to 25°C for 7 days prior to use.

Other study drugs (e.g., TM buprenorphine) should be stored according to the label.

Temperature excursions outside of the defined ranges should be reported to the Sponsor, the product should be immediately quarantined and used only if/after Sponsor approval has been obtained (see Pharmacy Manual).

The study drugs must be handled strictly in accordance with the protocol, applicable product labelling information, Pharmacy Manual, and applicable local laws and regulations.

9.2 Packaging and Labelling

The RBP-6000 clinical study labels will be developed in accordance with Good Manufacturing Practice and local regulatory requirements. Detailed information regarding the commercial packaging of RBP-6000 is outlined in the applicable product labelling information.

RBP-6000 will be supplied by the Sponsor as a single, pre-filled syringe, the inner packaging (pouch) must remain with the outer product carton until the time of administration.

9.3 Shipment

RBP-6000 will be shipped under monitored refrigerated temperatures between 2ºC to 8ºC (35.6°F to 46.4°F).

9.4 Method of Assigning Participants to Treatment Groups

When a participant signs the ICF, she/he will be assigned a unique participant number via Interactive Voice/Web Response System (IXRS) in numerical sequence, which will be used for the duration of the study. The participant number will be recorded in the source documentation.

9.4.1 Randomisation into the Open-label Induction Sub-study

The sub-study randomisation will be implemented using an IXRS.

Qualified participants who meet all of the inclusion criteria, none of the exclusion criteria, and all of the TM buprenorphine dosing criteria will be randomised. Eligible participants will be randomised following the first induction day UDS, at a 2:1 ratio to receive either rapid induction or SoC induction. The induction randomisation number will

be assigned via the IXRS, using central, blocked, stratified randomisation schedules. The randomisation factor is first induction day UDS positive for fentanyl (yes or no).

Participants who are randomised but do not receive TM buprenorphine will not be replaced.

9.4.2 Randomisation into the DBTP

After receiving two 300-mg RBP-6000 doses given 1 week apart during the OLTP, eligible participants will be randomised on Week 6 immediately prior to their third injection (i.e., 4 weeks after their second 300-mg dose of RBP-6000), at a 1:1 ratio to receive either 300 mg RBP-6000 or 100 mg RBP-6000 for 8 SC injections, 1 injection every 4 weeks. The double-blind period randomisation number will be assigned via an IXRS, using central, blocked, stratified randomisation schedules. The 2 randomisation factors are:1) opioid use predominantly via injection route at Screening (yes or no) and 2) Week 6 UDS result for opioids (negative or positive).

9.5 Blinding

Participants, Investigators and site personnel not involved in performing injections of RBP-6000 will be blinded to study medication during the DBTP (Injections 3 to 10). The blinding of the study will be maintained through several mechanisms.

- An IXRS system will be used, which will track the randomisation for each study participant and will also assign the treatment that the participant will receive. The IXRS will be responsible for subsequent assignment of all RBP-6000 doses.

- Each study site will have an unblinded study drug manager and an unblinded drug administrator who will have no other responsibilities in the clinical trial. These roles can be fulfilled by the same or multiple individuals. The person who administers the treatment must be a healthcare provider, who is familiar with giving injections.

- At each injection visit in the DBTP (Injections 3 to 10), a unblinded staff member will contact IXRS to obtain the treatment assignment.

- The unblinded staff member will then obtain and prepare the RBP-6000 for administration. Because of volume and size differences between RBP-6000 containing 100 mg or 300 mg buprenorphine, study participants and site personnel must be shielded from seeing the syringe prior to and during the injection. The unblinded staff member will apply a large blank label around the barrel of the syringe several times, to mask the volume and size of the injection. RBP-6000 preparation will occur in a separate room away from blinded study staff and the participant.

- Once RBP-6000 has been prepared, the unblinded study drug administrator will administer RBP-6000 to the participant as described in the applicable product labelling information. RBP-6000 administered will be tracked via IXRS and drug accountability logs will be maintained for each participant, which the unblinded study drug manager will complete.

The Open-label Induction Sub-study will be open label.

9.6 Procedure for Breaking the Blind

The Investigator should not request the treatment assignment code unless knowledge of the participant's treatment is required for the participant's clinical care and safety. In the unlikely event that knowledge of the treatment assignment is necessary in order to treat a participant, the Investigator is encouraged to contact the medical monitor by telephone to discuss his/her rationale for unblinding. To prevent delays to the Investigator or medical personnel responding to a potentially emergent situation, unblinding of study medication will be done through the IXRS by the Investigator, and the medical monitor must be notified within 24 hours. Documentation of the breaking of the blind (intentional or unintentional) should be recorded in the participant's medical record with the date and time the blind was broken, and the names of the personnel involved. The assigned treatment should not be communicated to any members of the study team or site staff unless necessary to provide treatment for the participant. If any unblinding occurs, the medical monitor should be notified.

9.7 Dose and Administration

Eligible participants will be advised to abstain from short-acting opioids (such as morphine sulphate, oxycodone, hydromorphone, oxymorphone or codeine) for at least 6 hours and long-acting opioids (such as methadone or levorphanol) for at least 24 hours before arriving at the site on the morning of the first induction day. Eligible participants will be informed that under-reporting of the last use of opioids and undergoing induction with remaining exposure to opioids places them at higher risk for rapid and intense onset of withdrawal symptoms. Risk is increased with high doses of potent opioids, such as fentanyl, which may take longer to clear due to high lipophilicity, redistribution into fat, and prolonged excretion patterns (Mariani 2020). An on-site dipstick UDS at Screening to identify current opioids of abuse will support this discussion between the Investigator and study participant about the optimal period of abstinence for starting induction.

9.7.1 Transmucosal Buprenorphine

Participants are required to be in withdrawal (COWS ≥8) prior to administration of TM buprenorphine. The TM buprenorphine will be administered as per local prescribing information.

Participants experiencing exacerbated withdrawal symptoms post-TM buprenorphine will be treated symptomatically per the SAMHSA TIP 63 2020 guidelines (see Section 9.13 for treatment of withdrawal symptoms) and will be asked to remain in the clinic.

For participants in the rapid induction arm, if the participant does not meet RBP-6000 dosing criteria (see Section 4.1.2.1) after a minimum of 1 hour after receiving 4 mg TM buprenorphine, a second dose of 4 mg TM buprenorphine may be administered later that same day at the discretion of the Investigator to reattempt induction while the participant is still in the clinic. Alternatively, the participant may return to the site and repeat the induction process within 30 days of informed consent.

If a participant in the rapid induction arm experiences exacerbated withdrawal symptoms post RBP-6000 on Day 1, TM buprenorphine in increments of 2 to 4 mg up to a maximum dose of 12 mg (inclusive of pre–RBP-6000 TM buprenorphine) may be administered on Day 1 at the discretion of the Investigator to alleviate withdrawal symptoms while on site.

For participants in the SoC induction arm, TM buprenorphine may be administered and dispensed as per applicable product labelling information. Any doses of TM buprenorphine administered at the site, dispensed to the participant and taken by the participant outside of the clinic should be recorded. For reconciliation, participants will be asked to return any doses not taken as well as the empty packaging for all doses taken. The Investigator may ask the participant to return for dose adjustment as many times as necessary per SoC.

No participants are permitted to take home supplemental TM buprenorphine post the RBP-6000 injection on Day 1.

Time of dose is defined as the time the TM buprenorphine is placed into the oral cavity.

9.7.2 RBP-6000

RBP-6000 will be supplied by the Sponsor as a single, pre-filled syringe, the entire contents of which should be administered during a single SC injection by a healthcare provider as delegated by the Investigator.

To remain eligible to receive RBP-6000, participants must not display any of the following on assessment after the administration of TM buprenorphine: any allergic/hypersensitivity reaction to TM buprenorphine, precipitated withdrawal symptoms that would prevent RBP-6000 administration or sedation from the most recent TM buprenorphine received prior to RBP-6000 dosing, in the opinion of the Investigator.

RBP-6000 should be administered as per the Instructions for Use in the applicable product labelling information. After receiving two 300-mg RBP-6000 doses given 1 week (+4 days) apart (OLTP), eligible participants will be randomised immediately prior to their third injection, 4 weeks after their second 300-mg dose of RBP-6000, at a 1:1 ratio to receive either 300 mg RBP-6000 or 100 mg RBP-6000 for 8 SC injections, 1 injection every 4 weeks (-2/+4 days).

Time of dose for RBP-6000 is defined as the time the SC injection is complete. The time of dose and any dosing observations (e.g., partial doses or other issues with the injection) will be recorded in the source documentation; in addition, time of dose will be recorded in the eCRF.

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

RBP-6000 will be dispensed under the supervision of the Investigator, a suitably qualified member of the study team, or by a pharmacist after confirmation that the participant meets all eligibility and dosing criteria. The Investigator or designee agrees to neither administer RBP-6000 from, nor store it at any location other than the study site agreed upon with the Sponsor. Site personnel must maintain accountability records per the Pharmacy Manual.

9.8 Accountability

The Investigator is responsible for ensuring that all study drug received at the site is inventoried, accounted for and documented in accurate accountability records which will be provided to Indivior. All unused study drug will either be destroyed by the Investigator, as per local standard operating procedures (SOP) or returned to the clinical study drug distributor, as agreed with the sponsor. The study drug must be handled strictly in accordance with the protocol, Pharmacy Manual, Safety Data Sheet and the local prescribing information; it must be stored in a locked, limited-access area under appropriate environmental conditions.

All study drug dispensation will be performed by a pharmacist or designee, checked by a study site staff member and documented on a drug dispensation form.

Unused study drug must be available for verification by the site monitor during on-site monitoring visits.

9.9 Concomitant Therapies

Concomitant medications will be collected from Screening through the completion of the EOT visit. Any concomitant medications (including herbal preparations) taken during the

study will be recorded in the source documents and in the eCRF. Any changes in concomitant therapy during the study will be documented, including cessation of therapy, initiation of therapy and dose changes.

9.10 Prohibited Concomitant Therapies

Participants should be instructed to inform the Investigator or site staff of any medications, including over the counter products taken.

Participants are not permitted supplemental TM buprenorphine after they leave the site on Day 1.

Prescription use of additional buprenorphine (after Day 1), methadone or naltrexone for OUD is prohibited. The use of all prescription opioids should be avoided in this study. In the event that a participant is prescribed opioids for any reason, use should be captured as a concomitant medication and the Investigator should notify and discuss with the medical monitor if the participant should remain in the study.

9.11 Restricted Concomitant Therapies

Due to additive pharmacologic effects, the concomitant use of benzodiazepines or other central nervous system depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma and death. However, a 2017 FDA Drug Safety Communication noted that although concomitant use of buprenorphine or methadone with benzodiazepines increases the risk of an adverse reaction, including overdose death, opioid agonist treatment should not be denied to patients solely on the basis of their taking benzodiazepines, because untreated OUD can pose a greater risk of morbidity and mortality. The FDA advises that careful medication management by healthcare professionals can reduce risk (see www.fda.gov/downloads /Drugs/DrugSafety/UCM576377.pdf for more information).

The RBP-6000 prescribing information should be referenced regarding use of the below concomitant therapies.

- benzodiazepines and other central nervous system depressants
- cytochrome P450 3A4 inhibitors
- cytochrome P450 3A4 inducers
- antiretrovirals: non-nucleoside reverse transcriptase inhibitors
- antiretrovirals: protease inhibitors
- serotonergic drugs
- monoamine oxidase inhibitors
- muscle relaxants
- diuretics

- anticholinergic drugs

Contact the Indivior medical monitor if you have any questions or concerns if any enrolled participants initiating chronic treatment with any of these restricted medications.

9.12 Lifestyle Restrictions

Eligible participants will be advised to abstain from short-acting opioids (such as morphine sulphate, oxycodone, hydromorphone, oxymorphone or codeine) for at least 6 hours and long-acting opioids (such as methadone or levorphanol) for at least 24 hours before arriving at the site on the morning of RBP-6000 induction. Participants will be informed that under-reporting their last use of opioids and undergoing induction with remaining exposure to opioids places them at high risk for rapid and intense onset of withdrawal symptoms. Risk is increased with high doses of potent opioids, such as fentanyl; an on-site dipstick UDS at Screening to identify current opioids of abuse will support this discussion between Investigator and trial participant.

Eligible participants will be advised to abstain from alcohol throughout the study, as central nervous system depressants increase the risk of respiratory depression, profound sedation, coma and death in patients taking buprenorphine.

9.13 Permitted Concomitant Therapies

The Investigator may prescribe concomitant medications or treatments deemed necessary to the participant, except those medications defined in Section 9.10 and Section 9.11 of this protocol.

If the participant experiences withdrawal symptoms at any time (including withdrawal after RBP-6000), he/she may be treated symptomatically (SAMHSA TIP 63 2020):

- Nausea: ondansetron or metoclopramide
- Diarrhoea: loperamide
- Anxiety, irritability, sweating: clonidine
- Insomnia: diphenhydramine, trazodone
- Pain: nonsteroidal anti-inflammatory drugs

Participants who experience opioid withdrawal after RBP-6000 administration may be treated with non-opioid medications as described above.

For rapid induction participants, if precipitated withdrawal occurs post TM buprenorphine that would prevent RBP-6000 administration, an additional 4 mg TM buprenorphine may be re-administered later that same day at the discretion of the Investigator. Alternatively, the Investigator may permit the participant to return to the

facility on another day within 30 days of informed consent. Returning participants will repeat all Day 1 scheduled assessments. In addition for rapid induction participants, adjunctive use of TM buprenorphine in increments of 2 to 4 mg up to a maximum of 12 mg may be administered on Day 1 (i.e., 12 mg total TM buprenorphine on Day 1, inclusive of pre–RBP-6000 TM buprenorphine) at the discretion of the Investigator to alleviate withdrawal symptoms after the first injection of RBP-6000.

Investigators will be asked to identify concomitant medications administered to alleviate withdrawal symptoms.

Participants will not be discontinued from treatment due to non-prescribed opioid use (including TM buprenorphine), but use should be captured on the TLFB.

9.14 Compliance

All study treatments will be administered at the site, documented in the source and recorded in the eCRF.

RBP-6000 injection compliance will be assessed by inspecting the injection site for evidence of attempted removal of the depot by the participant, documented in the source. Likewise, surgical removal by a physician will be documented in the source and recorded in the eCRF. See Section 10.7 for details on reporting depot removal.

Use of prohibited concomitant medications will be evaluated per the concomitant medication assessment outlined in the Schedules of Events accessed via Table 2, documented in the source and recorded in the eCRF.

9.15 Reporting Product Complaints

The Investigator and study site staff are responsible for prompt recognition and reporting of product quality complaints to Indivior. A product quality complaint is any concern pertaining to the manufacturing or quality control of the study drug and includes, but is not limited to, e.g., short counts/empty pouches, leaking syringes, broken needles, labelling defects, missing inserts, packaging defects or difficult to open packaging, study drug that is thought to be ineffective, or has an appearance or odour that is outside of what is expected.

All product quality complaints should be reported to Indivior [redacted] in a timely manner and the following information provided:

- site number
- site contact/reported by
- kit number(s)

- participant number (if already assigned to a participant)
- description of issue
- picture, if available (photographs should be taken only if safe to do so/within site policy or practice to take photograph)

If the product has not yet been opened (i.e., product does not pose any hazard), retain the product and packaging in a quarantined space until further instruction is provided by Indivior. If the product is potentially hazardous, dispose per site process and document in the source.

9.16 Schedule of Assessments

Schedules of assessments are included in the appendices as detailed in Table 2.

Table 2 Schedules of Events

Appendix	Time Period
22.1	Schedule of Events – Screening (within 30 days prior to first induction day)
22.2	Schedule of Events – Rapid Induction Day 1 (Injection 1)
22.3	Schedule of Events – Standard of Care (SoC) Induction
22.4	Schedule of Events – Week 1 Day 2 to Week 16 – All On-site Visits
22.5	Schedule of Events – Week 18 to 36 – All On-site Visits
22.6	Schedule of Events – Week 38 to Week 40 End of Study and Early Termination

10 ADVERSE EVENTS

The Investigator or designee is responsible for identifying, documenting and reporting events that meet the definition of an AE.

An AE is any untoward medical occurrence in a participant associated with the use of a study drug regardless of the presence of a causal relationship to the study drug. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with a study drug, whether or not considered related to the study drug.

Events meeting the definition of an AE include:

- New condition detected after study drug administration even though the AE may have been present prior to receiving study drug.
- Exacerbation of a pre-existing condition (including intensification of a condition and/or an increase in frequency).
- Any abnormal laboratory test results or other safety assessments felt to be clinically significant in the opinion of the Investigator (including those that worsen from baseline).
- Symptoms and/or the clinical sequelae of a suspected interaction.
- Signs, symptoms or the clinical sequelae resulting from special interest conditions (see Section 10.1). Overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.
- Symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE.
- Symptoms and/or clinical sequelae that resulted in intervention.

Events that do not meet the definition of an AE include:

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedures; the condition that leads to the procedure is an AE.

- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, hospitalisation for elective surgery, hospitalisation for observation in the absence of an AE).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.1 AE of Special Interest

In this study an AE of special interest is:

- RBP-6000 depot removal (see Section 10.7)

This AE of special interest should be reported to Indivior, by the Investigator (or designee) **within 24 hours** from first being aware of the event, using the same reporting process as for SAEs, See Section 11.2.

For the first induction day/Day 1, Investigators also will be asked to identify any AEs that were associated with precipitated withdrawal, if based on their clinical judgment, precipitated withdrawal occurs.

10.2 Assessing and Documenting Adverse Events

The Investigator is ultimately responsible for assessing and reporting all AEs as outlined in the protocol. The assessment and reporting of AEs may be delegated to a medically qualified sub-Investigator, trained on this study protocol, who is listed on the delegation of authority log. All AEs regardless of treatment group or suspected causal relationship to the study drug will be reported as described in this protocol.

Adverse events should be volunteered by the participant or solicited from the participant using a standard statement, obtained from examination of the participant 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.

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 intensity (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 study drug-related or not, whether the AE is an opioid withdrawal symptom and whether a concomitant medication was given. This should be documented in the eCRF.

10.3 Time Period for Collecting Adverse Events

Adverse events will be collected from the time of signed informed consent until completion of the EOT/ET visit. Thereafter, participants will be contacted by telephone to assess AEs that were ongoing at the EOT/ET visit and concomitant medications associated with those ongoing AEs. Participants do not need to return to the site unless deemed medically necessary by the Investigator.

Participants with ongoing SAEs at the EOS telephone contact that, in the opinion of the Investigator, are associated with the study drug, will be followed and reported as described in Section 11. Participants with ongoing AEs at EOS telephone contact will not be followed up further.

10.4 Assessment of Intensity

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 participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

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; hospitalisation is probable

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

10.5 Assessment of Causality

The Investigator or a medically qualified sub-Investigator, trained on this study protocol, listed on the delegation of authority log is responsible for determining the AE relationship to the study drug.

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

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

Related: The cause of the AE is related to the study drug and cannot be reasonably explained by other factors (e.g., the participant's clinical state, concomitant therapy, and/or other interventions).

A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the study drug will be considered and investigated. The Investigator will also consult the applicable product labelling information in the determination of his/her assessment. For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE or AE of special interest has occurred and the Investigator has minimal information to include in the initial report to Indivior or designated representative. However, it is imperative that the Investigator always make an assessment of causality for every event prior to the initial transmission of the SAE or AE of special interest data to Indivior or designated representative. The Investigator may change his/her opinion of causality in light of follow-up information and amend the SAE or AE of special interest data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.6 Clinical Laboratory, Vital Signs, and Other Safety Findings

Changes in laboratory values, vital signs or other safety parameters (e.g., neurological and clinical symptom assessments) as noted in the protocol are a sub-set of AEs and are reportable only if the lab test result is associated with accompanying symptoms, and/ or requires additional diagnostic testing or intervention (medical, surgical), and/or requires additional significant treatment, and/or requires temporal or permanent discontinuation of study drug, or a change to dosing other than as permitted by protocol, or if considered to be clinically significant by Investigator or medically qualified designee.

Guidance for the procedures to follow for elevated liver function tests are provided in Appendix 22.7.

All ECG findings that are considered abnormal and clinically significant should be evaluated for a change from baseline and must be captured as AEs.

10.7 RBP-6000 Depot Removal

If clinically indicated, the RBP-6000 depot may be surgically removed within 14 days of injection. Any occurrence of depot removal will be captured in the database as an AE of special interest. In addition, the AE that resulted in the depot removal needs to be reported; this is not an AE of special interest. Additional details about the depot removal (e.g., the reason for the removal, whether the depot was removed by the participant or the Investigator, and whether this was voluntary or involuntary [i.e., whether the participant agreed to the removal]) also need to be reported. Depot removal should be reported using the same timing as for SAEs (see Section 11.2.1).

11 SERIOUS ADVERSE EVENT

11.1 Definition of Serious Adverse Event

The Investigator or designee is responsible for identifying, documenting and reporting events that meet the definition of an SAE.

An SAE is any event that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a participant who received RBP-6000
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalisation, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
    - intensive treatment in an emergency room or at home for allergic bronchospasm
    - blood dyscrasias or convulsions that do not result in inpatient hospitalisation
    - development of drug dependency or drug abuse
- Laboratory values of ALT or AST >3×ULN and bilirubin >2×ULN are defined as SAEs (important medical event), and should be reported to Indivior (or designated representative), by the Investigator (or designee) **within 24 hours** from first being aware of the event, using the same reporting process as for SAEs, See Section 11.2.1. Potential Hy's Law cases should be managed as described in 22.7.

An AE is considered "life threatening" if the participant was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, study drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though study drug-induced hepatitis can be fatal.

Any AEs requiring hospitalisation should be considered SAEs. Hospitalisation for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) should not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE (either "serious" or "non-serious") according to the usual criteria.

In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or other outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the participant's ability to carry out normal life functions.

11.2 Documenting Serious Adverse Events

When an SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostic reports) pertaining to the event. The Investigator will then record all relevant information regarding an SAE on the appropriate electronic or paper form(s).

It is not acceptable for the Investigator to send photocopies of the participant's medical records to Indivior in lieu of completion of the SAE Reporting Form. However, there may be cases where copies of medical records are requested by Indivior or designated representative. In this instance, all participant identifiers, with the exception of participant number, will be redacted on the copies of the medical records prior to submission to Indivior.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as an AE or SAE and not the individual signs/symptoms.

11.2.1 Investigator Reporting of Serious Adverse Events

Once the Investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to Indivior Global Safety (or designated representative) by the Investigator (or designee) **within 24 hours** from first being aware of the event. Any follow-up information on a previously reported SAE will also be reported to Indivior Global Safety within 24 hours. [redacted]

Where additional information is needed or expected, the Investigator will not wait to receive all information before reporting the event to Indivior. The Investigator must provide an assessment of causality at the time of the initial report as described in Section 10.5 of the protocol.

In the event of an SAE, the Investigator or designee will notify Indivior Global Safety by completing the appropriate form(s) in the eCRF. Follow-up information will also be reported in the eCRF.

In the event that the electronic data capture system is not available, a paper Safety Information Collection Form should be completed and submitted to Indivior Global Safety via email or fax:

When the electronic data capture system is again available, the information recorded on the paper Safety Information Collection Form should be entered into the eCRF.

11.2.2 Regulatory Reporting Requirements for Serious Adverse Events

Prompt receipt of notifications of SAEs to Indivior Global Safety (or designated representative) from Investigators is essential in ensuring that legal obligations and ethical responsibilities regarding the safety of participants are met.

Indivior has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug. Indivior Global Safety (or designated representative) will comply with country-specific regulatory requirements pertaining to safety reporting to Regulatory Authorities, IRBs/ECs and Investigators.

A suspected unexpected serious adverse reaction (SUSAR) is an SAE related to the study drug administered in any dose and that, in its nature or severity, is inconsistent with the applicable product labelling information. Indivior Global Safety (or designated representative) will determine if an SAE meets the definition of a SUSAR and distribute SUSAR reports according to country-specific regulatory requirements and Indivior policy. An Investigator who receives a safety report describing an SAE or other specific safety information (e.g., summary or line listing of SAEs, Dear Investigator Letter) will file it with the applicable product labelling information and will notify the IRB/EC, if required according to local requirements.

11.2.3 Overdosing with RBP-6000

Any instance of overdosing with RBP-6000 (e.g., participant received an additional dose of RBP-6000 before the appropriate dosing interval) must be communicated to the medical monitor **within 24 hours**. Details of any AEs associated with overdose or use of any concomitant medications used in managing those AEs should be recorded.

12 PREGNANCY

12.1 Collecting and Reporting Pregnancy Information

Information on all pregnancies will be collected from receipt of study drug until 3 months following the last dose of TM buprenorphine (for participants who receive only TM buprenorphine) and until 12 months following the last dose of RBP-6000 (approximately 6 to 8 terminal half-lives). All confirmed pregnancies that occur within this study will be followed until resolution (i.e., termination [voluntary or spontaneous] or birth).

Pregnancy of a study participant without associated unexpected or adverse sequelae is not a reportable AE, but must be reported to Indivior Global Safety (or designated representative) using the Safety Information Collection Form **within 24 hours** of the Investigator or designee first being aware of the pregnancy (contact details for reporting via email or fax are the same as for SAEs).

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and infant. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

Any pregnancy complication or elective termination for medical reasons must be reported as an AE or SAE. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the participant has completed the study and considered by the Investigator as possibly related to the study treatment, must be promptly reported to Indivior or designated representative. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of a pregnancy through spontaneous reporting.

12.2 Action to be Taken if Pregnancy Occurs in a Female Participant

If a female participant suspects that she is pregnant (e.g., missed period, self-administered pregnancy test) during treatment or within 12 months after the discontinuation of RBP-6000, treatment will immediately be withheld, where applicable.

If the participant is still participating in the study and suspects she is pregnant or has a positive urine pregnancy test at a visit, she will undergo a confirmatory serum pregnancy test at or before the next scheduled visit (prior to RBP-6000 injection). She will not receive any further treatment unless the pregnancy tests are confirmed negative.

If the result of the serum pregnancy test confirms the participant is pregnant, she will be discontinued from the study and will undergo all final study visit procedures (with the exception of any additional pregnancy testing); however, pregnant participants who have already received their final (10^{th}) RBP-6000 injection may continue to complete the study.

The Investigator should fully inform the female participant of potential risks to the foetus.

13 DATA MANAGEMENT

13.1 Data Collection and Management

Data captured in the eCRF will be combined with external data captured centrally outside of the eCRF (e.g., laboratory results) in a secured, access-controlled repository and comprise the clinical trial database. Clinical data will be managed in accordance with the data management plan to ensure that the integrity of the data is maintained. Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug). The eCRFs (including data queries and audit trails) will be retained by Indivior. Electronic copies of completed participant eCRFs will be sent to the Investigator to maintain for their records. Participant identifiers will not be collected or transmitted to Indivior according to Indivior standards and procedures. Data collection will be completed according to the study plans.

13.2 Database Quality Assurance

The eCRFs will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerised and manual procedures. Data queries requiring clarification may be generated by the study team and addressed by the investigational site. Only authorised personnel will make corrections to the eCRFs, and all corrections will be documented in an audit trail.

13.3 Source Documentation

The Investigator is responsible for the quality of the data recorded in the eCRF. The data recorded should be a complete and accurate account of the participant's record collected during the study.

[redacted] certain clinician administered assessments (e.g., COWS, TLFB) will be captured electronically via direct entry into devices provided to the sites. Data entered will be considered the source for these assessments.

All other study data will originate from 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 and 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 Investigator and made available for direct inspection by the authorised study personnel outlined in the ICF.

See also, Section 15.5, Study Files and Record Retention.

14 STATISTICS

Statistical analyses for the Open-label Induction Sub-study are detailed in Appendix 22.9.

14.1 General Procedures

This section describes sample size determination, analysis populations and planned analyses for efficacy and safety measures.

A statistical analysis plan (SAP) will be prepared after the protocol is approved and will be signed off before database lock occurs. The SAP will provide further details regarding analyses. Additional unplanned analyses may be required after all planned analyses have been completed. Any deviations from the analyses described below will be outlined in the SAP. Any unplanned analyses will be clearly identified in the clinical study report.

Continuous variables will be summarised using descriptive statistics such as mean, standard deviations (SD), median, interquartile range, minimum and maximum. Categorical variables will be reported as frequency counts (including number missing) and the percentage of participants in corresponding categories. Individual participant data will be presented by participant in data listings. Data listings will include all data collected from the initial Screening Visit to the EOS for all participants enrolled.

Buprenorphine plasma concentrations will be summarised at each scheduled time point. For summary purposes, buprenorphine plasma concentration values below the limit of quantification will be set to zero.

14.2 Statistical Hypothesis

For the primary efficacy objective, the primary endpoint is the proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 20 to 38.

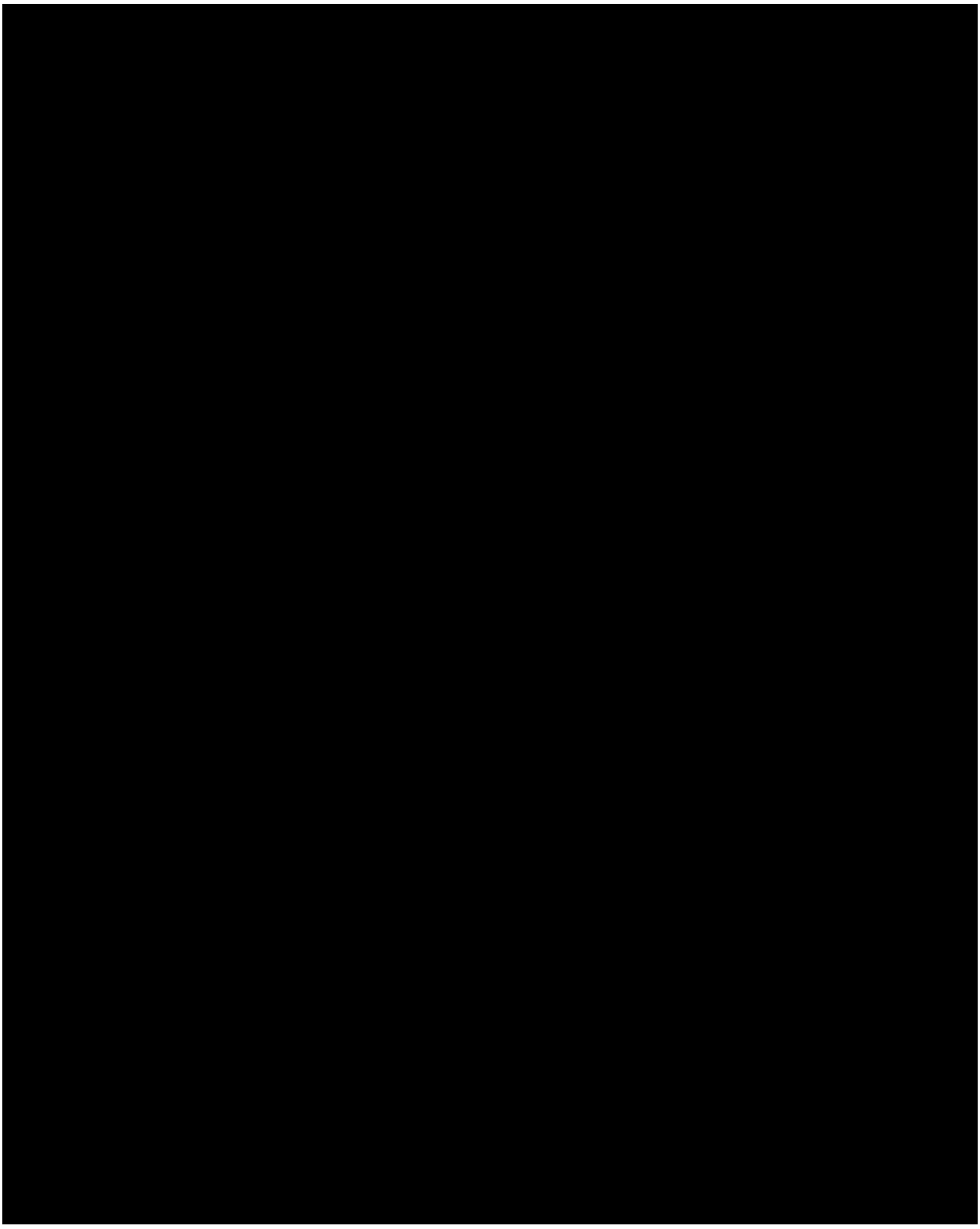
For the primary endpoint, the null and alternative hypotheses are

H_0: proportion of responders $_{300mg}$ = proportion of responders $_{100mg}$

H_A: proportion of responders $_{300mg}$ > proportion of responders $_{100mg.}$

14.3 Sample Size

[redacted]



14.4 Analysis Populations

14.4.1 Efficacy Analysis Population

The Full Analysis Set (FAS) will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomised participants who received at least 1 maintenance RBP-6000 injection post-randomisation. Participants will be included in the treatment group (RBP-6000 300/300 mg or RBP-6000 300/100 mg) to which they are randomised for the efficacy analysis.

14.4.2 Safety Analysis Populations

14.4.2.1 RBP-6000 Open-label Safety Population

The RBP-6000 Open-label Safety Population will be used for the safety analysis for the OLTP (during which every participant receives two 300-mg RBP-6000 injections). This population consists of all participants who received at least 1 post-enrolment open-label RBP-6000 injection.

14.4.2.2 RBP-6000 Double-blind Safety Population

The RBP-6000 Double-blind Safety Population will be used for the safety analysis for the randomised DBTP (i.e., the post-randomisation period). This population consists of all participants who received at least 1 maintenance RBP-6000 injection post-randomisation. For the DBTP, the participants will be analysed corresponding to the study treatment they actually received. For most participants, this will be the treatment group to which they are randomised. Any participant who receives incorrect study treatment for the entire DBTP will be included in the treatment group corresponding to the study treatment actually received.

14.4.4 Sub-study

For details on analysis populations for participants in the Open-label Induction Sub-study, see Appendix 22.9.

14.5 Demographic and Disease Characteristics

Demographic and disease characteristics at Screening, (e.g., sex, race, age, weight, height, tobacco use, alcohol use, caffeine use, prior medications, history of drug use, route of opioid use, overdose history, medical and psychiatric history, and MOUD) will be summarised for FAS population, TM Buprenorphine Safety Population, and RBP-6000 Safety Population by treatment group using descriptive statistics. Qualitative variables, (e.g., sex, race) will be summarised using frequencies; quantitative variables (e.g., age, weight, height) will be summarised (e.g., using mean, SD, median, minimum and maximum).

14.6 Efficacy Analysis

14.6.1 Definition of Baseline

For change from baseline efficacy analyses, 3 baselines are defined. For each endpoint, the applicable baseline(s) will be specified in the protocol or SAP.

- Screening – the value collected at the Screening Visit.

- Pre–Open-label Injection baseline – the last value prior to the first RBP-6000 injection in the OLTP.

- Pre–Double-blind Injection baseline – the last value prior to the first RBP-6000 injection in the DBTP.

14.6.2 Primary and Secondary Estimands

The primary and secondary estimands are presented in Table 5.

The primary estimand aligns with the primary objective of the study. The primary endpoint,

- Proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 20 to 38 (inclusive)

aligns with endpoint recommendations in the FDA Guidance for Industry *Opioid Use Disorder: Developing Depot Buprenorphine Products for Treatment* (FDA 2019).

- The endpoint measures a decrease in the use of opioids.

- The endpoint is defined using an initial timepoint of Week 20. This 20-week interval incorporates a grace period as noted in the guidance (i.e., the 6-week OLTP) which allows participants time for engagement in treatment, plus 14 weeks post-randomisation to allow for sufficient separation between the treatment groups with respect to plasma concentrations of buprenorphine.

- For proportion of responders for weekly opioid use, missing visits following treatment discontinuation and skipped visits missing opioid use assessment are considered positive for opioid use and are reflected in the composite strategy for intercurrent events (IE).

- The primary endpoint is a responder definition, as per the guidance.

The population will be the FAS, consisting of all randomised participants who receive at least 1 RBP-6000 injection post-randomisation. This population will represent the complete randomised population with the exception of participants who are randomised but do not receive randomised treatment (which is typically a rare occurrence).

The intercurrent events strategy (IES) is a composite strategy to address the IE of discontinuation from the treatment/study and skipped injection/visit. Under the strategy,

missing UDS + TLFB assessments at a visit (i.e., both are missing) due to these IEs are imputed as positive for opioid use. In addition to aligning with the FDA guidance, this composite strategy is considered appropriate in that participants who discontinue from the study or miss an injection or a visit can reasonably be assumed to have returned to using opioids for that timeframe (i.e., missing visits imputed as positive for opioid use). Therefore, in accordance with the composite strategy, the IE is incorporated into the endpoint via this imputation.

The population-level summary statistic is the ratio or difference of the treatment group proportions. The estimates of the ratios will be unadjusted and will account for the stratified randomisation employed in the study. In addition, a supportive risk-adjusted estimation will be provided to adjust for baseline factors potentially impacting treatment response.

The primary sensitivity estimand has the same attributes as the primary estimand, except that the composite strategy for addressing IEs will utilise a multiple imputation method to impute monotone missing data due to discontinuation from the study. This estimand will allow evaluation of the primary estimand IES.

Table 5 Primary and Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	**Population**	**IES**	**PLS (Analysis)**
Primary Objective: To compare the efficacy of 100-mg and 300-mg maintenance doses of RBP-6000 administered every 4 weeks in participants who use opioids via an injection route and/or use high doses of opioids				
Primary Efficacy Endpoint	Proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 20 to 38 (inclusive)	Study population: OUD treatment-seeking patients who use opioids via an injection route and/or use high doses of illicit opioids. Analysis population: FAS	Composite strategy: Visits with missing opioid assessments, i.e., missing both UDS and TLFB due to discontinuation from the study (monotone missing) or due to skipped visit (intermittent missing), will be imputed as "positive" for opioid use (i.e., worst-case outcome)	Cochran-Mantel-Haenszel test stratified for RF to provide the unadjusted treatment group comparison Ratio/difference of the responder proportions (300 mg vs. 100 mg) will be estimated using non-parametric ANCOVA accounting for randomisation stratification to provide the 95% CI for unadjusted estimation Non-parametric ANCOVA to account for randomisation stratification and to adjust for factors at Screening or randomisation baseline potentially related to the primary endpoint (age, gender, alcohol and tobacco use, years of [injection route] opioid use, and concomitant non-opioid drug use [e.g., cocaine]) to provide the 95% CI for risk-adjusted estimation

Table 5 Primary and Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	**Population**	**IES**	**PLS (Analysis)**
Primary Efficacy Endpoint Sensitivity	As primary	As primary	Composite strategy: The monotone missing opioid usage assessment will be imputed using logistic regression method separately within each treatment group, under a missing at random assumption. The imputation model will include the RF and baseline factors used for the non-parametric ANCOVA. Fifty imputation data sets will be generated to draw statistical inference. Intermittent missing assessments will be imputed using Markov chain Monte Carlo method to produce monotone missingness or using the worst-case outcome of the observed result immediately before and after the missing value.	As primary for each imputed dataset

Table 5 Primary and Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	**Population**	**IES**	**PLS (Analysis)**
Secondary Efficacy Endpoint 1	Participants' percentage of days opioids were used out of days assessed (TLFB) over Weeks 10 to Week 38 (inclusive)	As primary	While-on-treatment strategy Missing daily TLFB (monotone or intermittent) will not be imputed. For the participant who has an injection of randomised treatment but without any TLFB assessed post-randomisation (typically a rare occurrence), participant's percentage of days opioids were used will be derived based on his/her last observed TLFB prior to the randomisation, i.e., the TLFB for 7-day opioid use at the randomisation visit or the last observed TLFB after the first injection of RBP-6000 if the TLFB is also missing at the randomisation visit.	Wilcoxon rank-sum test stratified for RF to provide the unadjusted treatment group comparison Ratio/difference of the treatment group means (300 mg vs. 100 mg) will be estimated using non-parametric ANCOVA accounting for randomisation stratification to provide the 95% CI for unadjusted estimation Non-parametric ANCOVA to account for randomisation stratification and to adjust for factors at Screening or randomisation baseline potentially related to the endpoint (age, gender, alcohol and tobacco use, years of [injection route] opioid use, and concomitant non-opioid drug use [e.g., cocaine]) to provide the 95% CI for risk-adjusted estimation

Table 5 Primary and Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	**Population**	**IES**	**PLS (Analysis)**
Secondary Efficacy Endpoint 2	Proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 10 to 38 (inclusive)	As primary	As primary	As primary

Table 5 Primary and Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	**Population**	**IES**	**PLS (Analysis)**
Secondary Objective: To compare the efficacy of 100-mg and 300-mg maintenance doses of RBP-6000 administered every 4 weeks on treatment outcomes (e.g., treatment retention and harm reduction) in participants who use opioids via an injection route and/or use high doses of opioids				
Secondary 3	Percentage of visits with opioid abstinence (defined as negative UDS and TLFB for the prior week) over Weeks 10 to Week 38 (inclusive)	As primary	As primary	As secondary 1
Secondary 4	Proportion of responders for weekly opioid use, defined as - participants' percentage of visits with opioid abstinence being greater than or equal to 80% (for the last 5 visits planned for UDS and TLFB	As primary	Composite strategy: impute missing visits as positive	The proportion of responders will be compared between treatment groups using the unadjusted non-parametric ANCOVA approach accounting for randomisation stratification described in Section 14.6.3.2. The ratio/difference between treatment groups will be estimated with 95% CI.

Table 5 Primary and Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	**Population**	**IES**	**PLS (Analysis)**
	assessment over Week 30 to 38)			

Table 5 Primary and Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	**Population**	**IES**	**PLS (Analysis)**
Secondary 5	Proportion of responders for daily opioid use, defined as participants' percentage of days opioids were used out of days assessed (TLFB) being less than or equal to 20% for participants' last 5 visits with observed TLFB post randomisation.	As primary	While-on-treatment Missing data will not be imputed	As secondary 4
Secondary 6	Participants' percentage of visits with opioid abstinence (defined as negative UDS and TLFB for opioid use) overall (Week 2 to 38 inclusive)	As primary	As primary	As primary

Table 5 Primary and Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	**Population**	**IES**	**PLS (Analysis)**
Secondary 7	Participants' percentage of days opioids were used out of days assessed (TLFB) overall (Week 2 to 38 inclusive)	As primary	As secondary 1	As secondary 1
Secondary 8	Participants' percentage of days opioids were used via the injection route out of days assessed (TLFB) overall (Week 10 to 38 inclusive)	Analysis population: The participants who use opioids via the injection route for an average of ≥5 days per week in the last 4 weeks prior to Screening sub-population of the FAS	As secondary 1	As secondary 1
Secondary 9	Average number of times opioids were used per week (TLFB) by visit	As primary	While-on-treatment strategy Missing daily TLFB (monotone or intermittent) will not be imputed.	The average number of times opioids were used per week (TLFB) for each treatment group will be summarised by visit from Screening to Week 38 for overall and within individual randomisation stratum; the difference between treatment groups will be estimated with a 95% CI for each visit.

Table 5 Primary and Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	**Population**	**IES**	**PLS (Analysis)**
Secondary 10	Change in participants' number of times opioids were used per week from Screening or randomisation baseline to each visit	As primary	While-on-treatment strategy Only the participants with complete 7 daily TLFB information for a given visit will be analysed for that visit. As an alternative approach to handle missing data, a supplemental analysis will include participants with complete or partial daily TLFB information at the visit. The participants with partial daily TLFB information at a given visit will be imputed as number of times used opioid divided by the number of days with observed TLFB information times 7 for that visit.	The mean change value or percentage change value from Screening or randomisation baseline for each treatment group will be summarised by visit from Screening or randomisation baseline to Week 38 for overall and within individual randomisation stratum; the difference between treatment groups will be estimated with a 95% CI for each visit.
Secondary 11	Proportion of participants abstinent (defined as negative UDS and TLFB for opioid use) by visit.	As primary	While-on-treatment strategy Visit with missing opioid use assessments will not be imputed.	Proportion of participants abstinent will be estimated with 95% CI by visit for individual treatment groups from Screening to Week 38. The difference between the treatment groups will be estimated with 95% CI by visit
Secondary	Average number of	As primary	While-on-treatment strategy	The average number of days opioids were used

Table 5 Primary and Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	**Population**	**IES**	**PLS (Analysis)**
12	days opioids were used per week (TLFB) by visit		Missing daily TLFB (monotone or intermittent) will not be imputed.	per week (TLFB) for each treatment group will be summarised by visit from Screening to Week 38 for overall and within individual randomisation stratum; the difference between treatment groups will be estimated with a 95% CI for each visit.
Secondary 13	Treatment retention since randomisation	As primary	Not applicable: Intercurrent events are not relevant for this endpoint	Kaplan-Meier method to describe the survival curves.
Secondary 14	Proportion of randomised participants who complete the last scheduled injection of RBP-6000	As primary	Not applicable: Intercurrent events are not relevant for this endpoint	Difference between treatment groups in the proportion Non-parametric ANCOVA accounting for randomisation stratification to provide unadjusted estimation of the difference between treatment groups with 95% CI

ANCOVA=analysis of covariance; CI=confidence interval; DBTP=Double-Blind Treatment Period; FAS=Full Analysis Set; IES=intercurrent event(s) strategy; OUD = opioid use disorder; PLS=population-level summary; RF=randomisation factors; TLFB=TimeLine Follow Back; UDS=urine drug screen
The 2 RFs are:1) opioid use predominantly via injection route at Screening (yes or no) and 2) Week 6 UDS result (negative or positive for opioids).

14.6.3 Primary Efficacy Endpoint

14.6.3.1 Derivation of Opioid Use Combining UDS and TLFB for a Visit

For the primary endpoint (proportion of responders for weekly opioid use over Weeks 20 to 38), overall opioid use based on the 7 daily TLFB for the prior week at a visit will be derived according to Table 6, and opioid use at a visit combining UDS and overall TLFB opioid use will be derived according to Table 7.

Table 6 Overall TLFB Opioid Use Derivation Based on Daily TLFB Results at a Given Visit

	Daily TLFB Opioids		
	All Days = Missing	**All Non-missing Days = Did Not Use**	**Any Day = Used**
Overall TLFB Opioids	Missing	Negative	Positive

TLFB=TimeLine Follow Back

Table 7 Opioid Use Derivation Based on UDS and Overall TLFB Opioid Use Results at a Given Visit

		Overall TLFB Opioids		
		Missing	**Negative**	**Positive**
UDS Opioids	**Missing**	Missing	Negative	Positive
	Negative	Negative	Negative	Positive
	Positive	Positive	Positive	Positive

TLFB=TimeLine Follow Back; UDS=urine drug screen

14.6.3.2 Analysis

The primary objective will be evaluated for the FAS by comparing the RBP-6000 300/300-mg and the RBP-6000 300/100-mg groups on the primary endpoint:

- proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (defined as negative UDS and TLFB for opioid use) is greater than or equal to 80% over Weeks 20 to 38

(inclusive, based on 6 scheduled UDS and TLFB assessments and 4 planned random unscheduled UDS and TLFB assessments).

The percentage of visits with opioid abstinence for an individual participant will be derived as his/her number of visits with negative assessments divided by 10 (the number of the planned visits for opioid use assessments over Weeks 20 to 38), according to the composite IES. This is in fact to impute missing visits as positive. A participant with 8 or more opioid negative visits over Week 20 to 38 (i.e., greater than or equal to 80%) will be classified as a responder, otherwise as a non-responder.

A Cochran-Mantel-Haenszel (CMH) test stratified for randomisation factor will be performed to compare the 2 treatment groups on the primary endpoint.

The primary endpoint will be summarised using descriptive statistics. The ratio or difference of the responder proportions for 300 mg vs 100 mg will be presented within individual stratum and overall.

Supplementary analysis using the non-parametric randomisation-based covariance analyses (Koch 1998, Zink 2012) will be performed to account for the randomisation strata. The unadjusted ratio or difference of the responder proportions and 95% CI will be estimated.

Supplementary analysis using the non-parametric randomisation-based covariance analyses will also be performed to account for the randomisation strata and to adjust for risk factors at Screening and randomisation baseline potentially related to the primary endpoint (such as age, gender, alcohol and tobacco use, years of [injection route] opioid use, and concomitant non-opioid drug use [e.g., cocaine]). The risk-adjusted ratio or difference of the responder proportions and 95% CI will be estimated.

For the primary endpoint sensitivity estimand, the monotone missing opioid use assessment will be imputed using the logistic regression method separately within each treatment group, under a missing at random assumption. The imputation model will account for the randomisation stratification and adjust for the risk factors noted above. Intermittent missing assessments will be imputed using Markov chain Monte Carlo method to produce monotone missingness or using the worst-case outcome of the observed result immediately before and after the missing value. Fifty imputation data sets will be generated to draw statistical inference.

[redacted]

14.6.4 Secondary Efficacy Endpoint Analysis

Participants' percentage of days opioids were used out of days assessed (TLFB) over Weeks 10 to Week 38 (inclusive) will be based on the 7 daily TLFB for the prior week collected at the 9 scheduled and 6 random unscheduled visits. The overall opioid use percentage for an individual participant will be derived as his/her number of days of opioid use divided by the number of days with observed TLFB information, according to the while-on-treatment IES. Missing daily TLFB (monotone or intermittent) will not be imputed. For the participant who has an injection of randomised treatment but without any TLFB assessed post-randomisation (typically a rare occurrence), participant's percentage of days opioids were used will be derived based on his/her last observed TLFB assessment prior to the randomisation, i.e., the TLFB for the 7-day opioid use at the randomisation visit or the last observed TLFB after the first injection of RBP-6000 if the TLFB is also missing at the randomisation visit. A Wilcoxon ranksum (Van Elteren) test (van Elteren 1960) stratified for randomisation factor will be performed to compare the 2 treatment groups. The endpoint will be summarised using descriptive statistics. The cumulative distribution function by treatment group within individual stratum and overall will be graphically explored. The ratio or difference of the treatment group means for 300 mg vs 100 mg will be presented within individual stratum and overall. Supplementary analysis using the non-parametric randomisation based covariance analyses (Koch 1998, Zink 2012) will be performed to account for the randomisation strata. The unadjusted ratio or difference of the treatment group means and 95% CI will be estimated. Supplementary analysis using the non-parametric randomisation based covariance analyses will also be performed to account for the randomisation strata and to adjust for risk factors at Screening and randomisation baseline potentially related to the endpoint (such as age, gender, alcohol and tobacco use, years of [injection route] opioid use, and concomitant nonopioid drug use [e.g., cocaine]). The risk adjusted ratio or difference of the treatment group means and 95% CI will be estimated.

Proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 10 to 38 (inclusive), will be analysed in the same manner as the primary endpoint. The opioid abstinence percentage for an individual participant will be derived as his/her number of

visits with negative assessments divided by 15. A participant with 12 or more opioid negative visits over Week 10 to 38 (i.e., greater than or equal to 80%) will be classified as a responder, otherwise as a non-responder.

Participants' percentage of visits with opioid abstinence (defined as negative UDS and TLFB for opioid use) over Weeks 10 to 38 (inclusive, based on 9 scheduled UDS and TLFB assessments and 6 planned random unscheduled UDS and TLFB assessments). will use the composite IES to impute missing visits as positive. A Wilcoxon rank-sum (Van Elteren) test (van Elteren 1960) stratified for randomisation factor will be performed to compare the 2 treatment groups. The cumulative distribution function by treatment group within individual stratum and overall will be graphically explored and will compare various cut points for classifying a responder. The difference and ratio of responder rates for the 2 treatment groups will be described under the various cut points.

The responders for weekly opioid use will be based on participants' percentage of visits with opioid abstinence being greater than or equal to 80% for the last 5 visits planned for UDS and TLFB assessment over Week 30 to Week 38, using the composite IES to impute missing visits as positive. The opioid abstinence percentage for an individual participant will be derived as his/her number of visits with negative assessments divided by 5. A participant with 4 or more opioid negative visits over Week 30 to 38 (i.e., greater than or equal to 80%) will be classified as a responder, otherwise as a non-responder.

The responders for the daily opioid use will be based on the 7 daily TLFBs for the prior week collected at the last 5 observed visits post randomisation. The opioid use percentage for an individual participant will be derived as his/her number of days opioids were used divided by the number of days with observed TLFB information at those 5 visits post randomisation, according to the while-on-treatment IES with no imputation for missing data. For participants who have less than 5 visits with observed TLFB post randomisation, all available daily TLFB will be used to derive the opioid use percentage. A participant with 20% or less opioid use percentage will be classified as a responder, otherwise as a non-responder. The participant without observed daily TLFB will also be classified as non-responder.

The proportion of responders (for weekly and daily opioid use) will be compared between treatment groups using the unadjusted non-parametric ANCOVA approach accounting for randomisation stratification described in Section 14.6.3. The difference between treatment groups will be estimated with 95% CI.

The participants' percentage of visits with opioid abstinence (defined as negative UDS and TLFB for opioids use) overall (Week 2 to 38 inclusive) will be analysed in the same manner as the primary endpoint. In addition, this endpoint will be graphically presented using the cumulative distribution function.

The 2 secondary endpoints (participants' percentage of days opioids were used out of days assessed [TLFB] overall [Week 2 to 38 inclusive] and participants' percentage of days opioids were used via the injection route out of days assessed [TLFB] overall [Week 10 to 38 inclusive]) will be analysed in the same manner as secondary endpoint 2, except the analysis population for "used opioids via the injection route" will be those participants who use opioids via the injection route for an average of 5 or more days per week in the last 4 weeks prior to Screening sub-population of the FAS.

The average number of times opioids were used per week (TLFB) for a given visit within a treatment group will be based on the 7 daily TLFBs for the prior week collected at that visit, and calculated as the number of times opioids were used divided by the number of days with observed TLFB information for all participants within the group for that visit, then times 7. The endpoint will utilise a while-on-treatment IES with no imputation for missing data. The average value for each treatment group will be summarised by visit from Screening to Week 38 for overall and within individual randomisation stratum; the difference between treatment groups will be estimated with a 95% CI for each visit.

The change in participants' number of times opioids were used per week from Screening or randomisation baseline to each visit will be based on the 7 daily TLFB for the prior week collected at that visit. A "while-on-treatment" strategy will be used to address IEs, in that only the participants with complete 7 daily TLFB information for a given visit will be analysed for that visit. The mean change value or percentage change value from Screening or randomisation baseline for each treatment group will be summarised by visit from Screening or randomisation baseline to Week 38 for overall and within individual randomisation stratum; the difference between treatment groups will be estimated with a 95% CI for each visit. As an alternative approach to handle missing data, a supplemental analysis will include participants with complete or partial daily TLFB information at the visit. The participants with partial daily TLFB information at a given visit will be imputed as the number of times opioid were used divided by the number of days with observed TLFB information times 7 for that visit.

The proportion of participants abstinent (defined as negative UDS and TLFB for opioid use) for a given visit within a treatment group will be calculated as the number of participants abstinent (derived according to Table 6 and Table 7) divided by the number of participants with observed opioid use assessment for that visit. The average number of days opioids were used per week (TLFB) for a given visit within a treatment group will be calculated as number of days opioid were used divided by the number of days with observed TLFB information for all participants within the group for that visit, then times 7. Both endpoints will utilise a while-on-treatment IES with no imputation for missing data. The proportion or the average value for each treatment group will be summarised by visit from Screening to Week 38 for overall and within individual randomisation stratum; the difference between treatment groups will be estimated with a 95% CI for each visit.

The treatment retention since randomisation will be derived as the number of days from randomisation until the date of discontinuation. Participants who complete the study will be censored administratively at the EOT visit. The endpoint will be presented by treatment group for overall and within individual randomisation stratum using a Kaplan-Meier curve. Intercurrent events and missing data are not applicable for this endpoint.

The proportion of participants who complete the last scheduled injection of RBP-6000 at Week 34 will be compared between treatment groups using the unadjusted non-parametric ANCOVA approach accounting for randomisation stratification described in Section 14.6.3. The difference between treatment groups will be estimated with 95% CI. Intercurrent events and missing data are not applicable for this endpoint.

14.6.5 Exploratory Efficacy Endpoints Analysis

14.6.6 Subgroup Analysis

For the primary and secondary efficacy endpoints, the treatment difference between the RBP-6000 300/300-mg and the RBP-6000 300/100-mg groups and the corresponding 95% CI will be presented by the following subgroups:

- Race (Black or African American vs. non-Black or African American)
- Route of use (injection vs. non-injection)

Any additional subgroup analyses will be described in the SAP.

14.6.7 Multiplicity

There will be no multiplicity procedure applied across primary, secondary, and exploratory endpoints. Where statistical testing is performed, significance will be assessed at a nominal 2-sided 5% alpha-level.

14.7 Interim Analysis

No interim analyses are planned for the main study. For interim analyses in the Open-label Induction Sub-study, see Appendix 22.9.

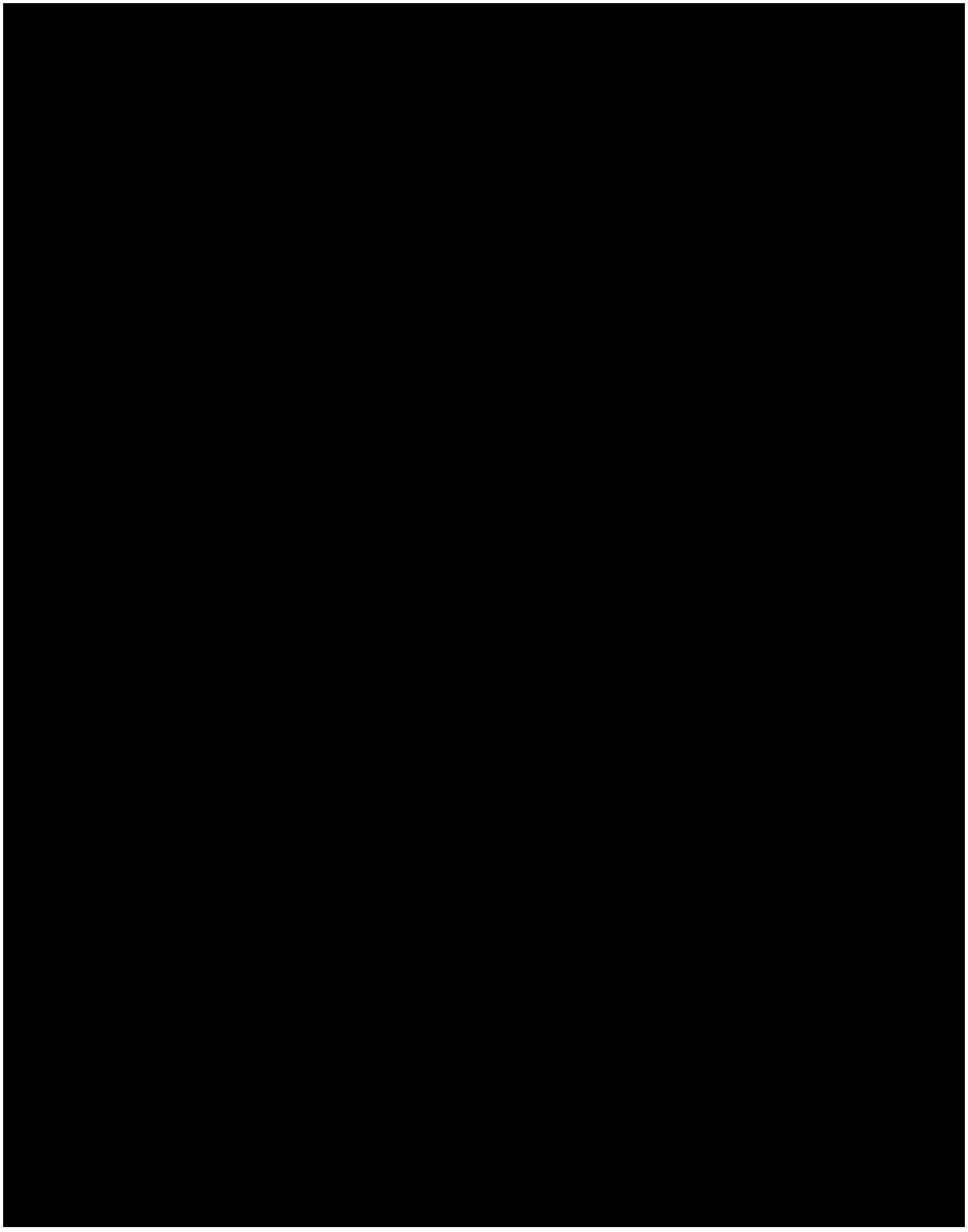
14.8 Handling of Missing Data

The missing value handling approach for the primary efficacy endpoint is described in Sections 14.6.2 and 14.6.3, for the secondary efficacy endpoints in Sections 14.6.2 and 14.6.4, for the exploratory efficacy endpoints in Section 14.6.5 [redacted]. Details for the missing data handling approach(es) for the other analyses will be described in the SAP.

No imputation of missing values will be performed for the safety analysis.

14.9 Other Statistical Considerations

[redacted]



14.9.3 Sub-study Analysis

For details on the statistical plan for the Open-label Induction Sub-study, see Appendix 22.9.

14.10 Safety Analysis

Safety data will be analysed using descriptive statistics for continuous endpoints and frequency counts with percentages for categorical endpoints. For RBP-6000 Open-label and Double-blind Safety Populations, safety data will be assessed by treatment group and overall for the OLTP and for the DBTP. The TM Buprenorphine Safety Population will also be used for summarising safety measures for the induction period. Complete details of the safety analyses will be provided in the SAP.

14.10.1 Adverse Events

Adverse events will be coded using MedDRA and grouped by system organ class. Events will be summarised with frequency and percentage, by system organ class and preferred term, by treatment group and overall for the DBTP and for the OLTP. Separate summaries will be provided for all TEAEs, drug-related TEAEs, serious TEAEs, TEAEs leading to discontinuation of study treatment, TEAEs associated with opioid withdrawal per the Investigator assessment, and TEAEs of special interest. TEAEs identified as injection site reactions and hepatic disorders using customised MedDRA queries will also be summarised. Details of the customised MedDRA queries will be provided in the SAP.

The incidence of deaths will also be reported and the primary causes of death summarised for the DBTP and the OLTP.

For details on TEAE assessment in the Open-label Induction Sub-study, see Appendix 22.9.

14.10.2 Extent of Exposure

The number of participants administered RBP-6000 will be summarised according to the duration of treatment. The total number of RBP-6000 injections will be presented as a continuous summary and a categorical summary. The cumulative dose/injections of RBP-6000 will also be summarised by dose level (100 mg or 300 mg). The number of participants who had early surgical removal of the RBP-6000 depot will be summarised. The TM buprenorphine dose during the induction period will also be summarised.

14.10.3 Other Safety Variables

The results of scheduled assessments of laboratory tests (haematology, chemistry and urinalysis), body weight, vital signs, 12-lead ECG, and concomitant medications will be summarised by treatment group and overall for the DBTP and for the OLTP. Further details will be provided in the SAP.

15 ETHICS AND RESPONSIBILITIES

15.1 Good Clinical Practice

Prior to site activation, Indivior or designated representative will obtain approval/favourable opinion from the relevant regulatory agency(ies) to conduct the study in accordance with ICH GCP and any applicable country-specific regulatory requirements.

The study will be carried out in accordance to the protocol and with local legal and regulatory requirements, ICH GCP and all applicable participant privacy requirements.

15.2 Data and Safety Monitoring Committee

There will be no data and safety monitoring committee for this study.

15.3 Institutional Review Board/Independent Ethics Committee

The protocol, ICF(s) and any other written information and/or materials to be provided to participants will be reviewed by an independent and appropriately constituted IRB/IEC. If required by local regulations, the protocol should be re-approved by the IRB/IEC annually. The IRB/IEC must be constituted and operate in accordance with the principles and requirements of ICH GCP.

Study drug can only be released to the Investigator after documentation that all ethical and legal requirements for starting the study has been received by Indivior or designated representative.

15.4 Informed Consent

The Investigator or a person designated by the Investigator (if allowed by local regulations) is to obtain written informed consent (including electronic consent) from each participant prior to entering the study. All written informed consent documents are required to have been reviewed and received a favourable opinion/approval from an IRB/IEC prior to presenting them to a potential participant.

Any changes to the ICF must be reviewed by Indivior before submission to the IRB/IEC.

The written informed consent process will include the review of oral and written information regarding the purpose, methods, anticipated duration and risks involved in study participation. The Investigator is to ensure that each participant is given the opportunity to ask questions and allowed time to consider the information provided. The Investigator or a person designated by the Investigator must also explain to each

participant that participation is voluntary and that consent can be withdrawn at any time and without reason. Participants will receive a signed and dated copy of the signed ICF before any study-specific procedures are conducted.

In the event that new safety information emerges that represents a significant change in the risk/benefit assessment, the ICF should be updated accordingly. All participants should be informed of the new information, provide their consent to continue in the study, and be provided with a signed and dated copy of the revised signed ICF.

15.5 Study Files and Record Retention

The Investigator must maintain all study-related records (except for those required by local regulation to be maintained elsewhere) in a safe and secure location throughout the conduct and following the closure of the study. The records must be accessible upon request (e.g., for an IRB/IEC, Indivior or regulatory inspection) along with the facility, study personnel and supporting systems/hardware. All documents pertaining to the study, including all versions of the approved study protocol, copy of the ICF and other documents as required per local laws and regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] documents), completed CRFs, source records (participant records, participant diaries, hospital records, laboratory records, drug accountability records, etc.), and other study-related materials will be retained in the permanent archives of the study site.

Where permitted by local laws and regulations, records may be maintained in a format other than hard copy (e.g., electronically in an electronic medical records system). The Investigator must ensure that all reproductions are an accurate legible copy of the original and that they meet necessary accessibility and retrieval standards. The Investigator must also ensure that a quality control process is in place for making reproductions and that the process has an acceptable back-up of any reproductions.

The minimum retention time for retaining study records will be in accordance with the strictest standard applicable for the study site as determined by local laws, regulations or institutional requirements. At a minimum, records will be maintained in accordance with local regulations. If the Investigator withdraws from the study (e.g., relocation, retirement) all study-related records should be transferred, in a written agreement with Indivior, to a mutually agreed upon designee within Indivior-specified timeframe.

16 AUDITING AND MONITORING

The purpose of an audit or regulatory inspection is to verify the accuracy and reliability of clinical study data submitted to a regulatory authority in support of research or marketing applications, and to assess compliance with statutory requirements regulations governing the conduct of clinical study.

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

The clinical monitor(s) will contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel. In accordance with applicable regulations and GCP guidelines, the Investigator shall make available for direct access all study-related records upon request by Indivior, Indivior's agents, clinical monitor(s), auditors, and/or IRB/IEC. The monitors will visit the site during the study in addition to maintaining frequent telephone and written communication. The extent, nature, and frequency of on-site monitoring 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.

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

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

This study will be organised, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines.

In accordance with the standards defined in Indivior SOPs and applicable regulatory requirements, clinical studies sponsored by Indivior are subject to Indivior Quality Assurance Investigator Site Audits that may be delegated to a contract research organisation or Indivior contract auditors. Investigator Site Audits will include review of, but are not limited to, drug supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The Investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner. Full consultation with the Investigator will be made prior to and during such an audit, which will be conducted according to Indivior's or a contract research organisation's Quality Assurance SOPs. In addition, this study is 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 Indivior immediately if this occurs and must fully cooperate with the inspection conducted at a reasonable time in a reasonable manner.

17 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Indivior. A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the Investigator must await approval before implementing the changes. Indivior or designated representative will submit substantial protocol amendments to the appropriate Regulatory Authorities for approval.

If in the judgment of the IRB/IEC, the Investigator, and/or Indivior, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the participant and/or has an impact on the participant's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for participants enrolled in the study before continued participation, based on IRB/IEC determination.

18 STUDY REPORT AND PUBLICATIONS

A clinical study report will be prepared following completion of the study. An Investigator signatory may be identified for the approval of the report if required by applicable regulatory requirements.

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

19 STUDY DISCONTINUATION

Both Indivior and the Investigator reserve the right to terminate the study at the Investigator's site at any time. Should this be necessary, Indivior, or a specified designee will inform the appropriate Regulatory Authorities of the termination of the study and the reasons for its termination, and the Investigator will inform the IRB/IEC of the same. In terminating the study, Indivior and the Investigator will assure that adequate consideration is given to the protection of the participants' interests.

20 CONFIDENTIALITY

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

Each participant will be identified by an assigned participant identification number when reporting study information to any entity outside of the study site. Data containing participant identification will not be removed from the study site without first redacting participant identifiers.

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22 APPENDICES

22.1 Schedule of Events – Screening (within 30 days prior to first induction day)

Procedure/Assessment	Screening	[redacted]	
Informed Consent[1]	X		1. Written informed consent must be obtained before any study-specific assessments/procedures are initiated. 2. Medical/psychiatric history will be obtained, including documented history of moderate or severe OUD as defined by DSM-5. Substance use history to include tobacco and caffeine use; alcohol use; drugs of abuse; and OUD history including any detox or prior medication for OUD, and any overdose history. 3. Complete physical examination to include an assessment of general appearance, skin and extremities, head and neck, lymph nodes, eyes, ears, nose, throat, thyroid, neurological system, lungs, cardiovascular system and abdomen (liver and spleen). The examination will not include a breast, pelvic or rectal exam, unless clinically indicated. 4. Includes systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature after the participant has been in a sitting position for at least 3 minutes. 5. A 12-lead ECG will be collected after the participant has been in a supine position for at least 5 minutes and before collecting blood samples. 6. The HIV-1/HIV-2, Hep B and Hep C antibody testing to be performed only in the absence of a positive (documented) medical history for these conditions. 7. Screening labs may be drawn any time during the Screening Period. Note that liver function test results are required to evaluate eligibility criteria prior to TM buprenorphine dosing. Approval from the sponsor must be obtained for any local laboratory and the laboratory normal ranges utilized to determine eligibility for screening. If a local laboratory is utilized for eligibility, the laboratory samples will also be sent to the central laboratory for the
Demographics	X		
Medical/Psychiatric/Substance Use History[2]	X		
Physical Examination[3]	X		
Height/Weight/BMI	X		
Vital Signs[4]	X		
12-Lead ECG[5]	X		
HIV-1/HIV-2, Hep B, Hep C Antibody[6,7]	X		
Serum Chemistry and Haematology, Urinalysis, PTT/PT/INR[7]	X		
UDS[8]	X		
Self-Reports/TLFB[9] [redacted]	X		
COWS	X		
Urine Pregnancy Test[11]	X		
AE Assessment	X		
Concomitant Medications[12]	X		
Counselling[13]	X		
Inclusion/Exclusion Criteria	X		
[redacted]		X[14]	

Procedure/Assessment	Screening	Health and Economic Outcomes	
			baseline analysis value. 8. Qualitative on-site dipstick to be performed. Investigator to discuss any positive UDS results with participant after the completion of the TLFB. 9. Details participant's drug use for each of the past 7 days, in addition to capturing the main route of use (and more specifically, if an injectable route was used), and number of times used each day. [redacted]. 11. Required for female participants of child-bearing potential only. Participants with positive pregnancy tests (urine test confirmed by serum test) during Screening and pre-induction will be discontinued. 12. Includes a review of any previous (taken within 30 days of providing written informed consent) and ongoing medications, including over-the-counter medications and herbal supplements. 13. Counselling to be provided including a detailed discussion on what to expect during induction, and ensuring the participant is informed that under-reporting of the last use of opioids puts him/her at higher risk for rapid and intense onset of withdrawal symptoms.

AE=adverse event; BMI= body mass index; COWS=Clinical Opiate Withdrawal Scale; D=day; ECG=electrocardiogram; [redacted] thromboplastin time; TLFB=TimeLine Follow Back; UDS=urine drug screen; [redacted]

22.2 Schedule of Events – Rapid Induction Day 1 (Injection 1)

Visit Name (Window)	**First Induction Day[1] / Repeat Induction Day**				**Week 1 Day 1**				
Timepoint	**Check in[2]**	**Pre-TM BUP**	**TM BUP**	**Post- TM BUP**	**Pre–RBP-6000**	**RBP-6000**	**Post RBP-6000**		
Planned Time			**-1 hr**			**0 hr**	**1 hr**	**2 hr**	**4 hr**
Urine Pregnancy Test[3]	X								
UDS[4]	X								
Self-Reports/TLFB[5]	X								
COWS[6]	X			X[7]			X	X	X
AE Assessment and Concomitant Medications[8]	←								→
Dosing Criteria	X[9]			X[10]					
Open-Label Randomisation[11]	X								
[redacted]									
Vital Signs[13]		X			X[14]				
12-Lead ECG[15]		X							
TM Buprenorphine Administration[16]			X						
[redacted]									
300-mg RBP-6000 Administration						X			
Injection Site Evaluation[19]							X	X	
[redacted]									
Counselling[20]	←								→

AE=adverse event; COWS=Clinical Opiate Withdrawal Scale; ECG=electrocardiogram; [redacted] TLFB=TimeLine Follow Back; TM=transmucosal; UDS=urine drug screen

1. See Figure 3 for rapid induction Day 1 induction flow chart.
2. Procedures are the same for all participants before randomisation (see flow chart in Figure 2).
3. Required for female participants of child-bearing potential only. Participants with positive pregnancy tests (urine test confirmed by serum test) will be discontinued. Participants having same-day screening and induction visits are not required to repeat the test for the induction visit.
4. Qualitative on-site dipstick to be performed. Investigator to discuss any positive UDS results with participant after the completion of the TLFB. Participants having same-day screening and induction visits are not required to repeat the test for the induction visit.
5. Details participant's daily drug use for each of the past 7 days, in addition to capturing the main route of use (and more specifically, if an injectable route was used), and number of times used per day.
6. Per Investigator discretion, participants with COWS <8 may either remain at the site and repeat assessments later that same day or be re-scheduled to return on another date. The COWS performed at 1 and 2 hours post-dose are to be performed ±15 minutes. Additional COWS may be repeated at any time, per Investigator discretion. Participants having same-day screening and induction visits are required to complete all the required COWS assessments for each visit, per the schedule of events (i.e., screening, induction check-in, post TM-BUP, and post RBP-6000).
7. To be completed ≥60 minutes after TM buprenorphine administration to assess for withdrawal symptoms. Participants experiencing withdrawal symptoms will be treated as clinically warranted (see Section 9.13). Participants experiencing precipitated withdrawal from TM buprenorphine that would prevent RBP-6000 administration may either remain in the clinic to repeat 4 mg TM buprenorphine later that same day or may return to the site and repeat the induction within 30 days of informed consent.
8. Includes a review of any previous (taken since the Screening Visit) and ongoing medications, including over-the-counter medications and herbal supplements.
9. See Section 5.6 for TM buprenorphine dosing criteria. Participants who meet the dosing criteria will be randomised; participants who do not meet the dosing criteria will either be asked to remain at the site or return to the site on another day. The 1st day of the repeat induction should be scheduled within 30 days of informed consent.
10. See Section 4.1.2.1 for RBP-6000 dosing criteria.
11. Randomisation 2:1 to either rapid or SoC induction. Note that participant must meet TM buprenorphine dosing criteria and have UDS result for fentanyl (negative or positive) available prior to randomisation.

[redacted]

13. Includes systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature after the participant has been in a sitting position for at least 3 minutes. Participants having same-day screening and induction visits are not required to repeat the vital signs for the induction visit.
14. Assessments will be completed on Day 1 prior to RBP-6000 injection once it has been determined that the participant will proceed with receiving the injection (i.e., meets RBP-6000 dosing criteria).
15. A 12-lead ECG will be collected after the participant has been in a supine position for at least 5 minutes and before collecting blood samples. Participants having same-day screening and induction visits are not required to repeat the ECG for the induction visit.
16. Additional TM buprenorphine in increments of 2 to 4 mg may be administered at the discretion of the Investigator (maximum total of 12 mg TM buprenorphine on Day 1, inclusive of any pre–RBP-6000 doses administered).

[redacted]

19. Injection site will be evaluated and any injection site reactions or infections will be recorded as AEs.
20. Participants will receive counselling during the treatment period.

22.3 Schedule of Events – Standard of Care (SoC) Induction

Visit Name (Window)	First Induction Day - TM Buprenorphine Induction							Dose Adjustment Day(s)	W1 D1				
Timepoint	Check in[1]	Pre-TM BUP	TM BUP	Post TM BUP					Pre–RBP-6000	RBP-6000	Post RBP-6000		
Planned Time				1 hr	2 hr	3 hr	5 hr			0 hr	1 hr	2hr	4 hr
Urine Pregnancy Test[2]	X								X				
UDS[3]	X								X				
Self-Reports/TLFB [4]	X								X				
COWS[5]	X			X[6]	X	X	X		X		X	X	X
AE Assessment and Concomitant Medications[7]	←												→
Dosing Criteria	X[8]								X[9]				
Open-Label Randomisation[10]	X												
[redacted]													
Vital Signs[12]		X							X				
12-Lead ECG[13]		X							X				
TM Buprenorphine Administration[14]			X	←			→	X					
TM Buprenorphine Dispensation[14]							X	X					
[redacted]													
300-mg RBP-6000 Administration										X			
Injection Site Evaluation[18]											X	X	
[redacted]													

Visit Name (Window)	First Induction Day - TM Buprenorphine Induction							Dose Adjustment Day(s)	W1 D1				
Timepoint	Check in[1]	Pre-TM BUP	TM BUP	Post TM BUP					Pre–RBP-6000	RBP-6000	Post RBP-6000		
Planned Time				1 hr	2 hr	3 hr	5 hr			0 hr	1 hr	2hr	4 hr
Counselling[19]	◄												►

AE=adverse event; BUP=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; d=day; ECG=electrocardiogram; [redacted] TLFB=TimeLine Follow Back; TM=transmucosal; UDS=urine drug screen

1. Procedures are the same for all participants before randomisation (see flow chart in Figure 2).
2. Required for female participants of child-bearing potential only. Participants with positive pregnancy tests (urine test confirmed by serum test) will be discontinued. Participants having same-day screening and induction visits are not required to repeat the test for the induction visit.
3. Qualitative on-site dipstick to be performed. Investigator to discuss any positive UDS results with participant after the completion of the TLFB. Participants having same-day screening and induction visits are not required to repeat the test for the induction visit.
4. Details participant's daily drug use for each of the past 7 days, in addition to capturing the main route of use (and more specifically, if an injectable route was used), and number of times used.
5. Per Investigator discretion, participants with COWS <8 may either remain at the site and repeat assessments at later that same day or be re-scheduled to return on another date. The COWS performed at 1 and 2 hours post-dose are to be performed ±15 minutes. The COWS may be repeated at any time, per Investigator discretion. Participants having same-day screening and induction visits are required to complete all the required COWS assessments for each visit, per the schedule of events (i.e., screening, induction check-in and post TM-BUP).
6. To be completed ≥60 minutes after TM buprenorphine administration to assess for withdrawal symptoms. Participants experiencing withdrawal symptoms will be treated as clinically warranted (see Section 9.13).
7. Includes a review of any previous (taken since the Screening Visit) and ongoing medications, including over-the-counter medications and herbal supplements.
8. See Section 5.6 for TM buprenorphine dosing criteria. Participants who do not meet the dosing criteria will either be asked to remain at the site or return to the site on another day. The 1st day of the repeat induction should be scheduled within 30 days of informed consent.
9. See Section 4.1.2.2 for RBP-6000 dosing criteria.
10. Participants will be randomised to either rapid or SoC induction. Note that participant must meet TM buprenorphine dosing criteria and have UDS result for fentanyl (negative or positive) available prior to randomisation.

[redacted]

12. Includes systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature after the participant has been in a sitting position for at least 3 minutes. Participants having same-day screening and induction visits are not required to repeat the vital signs for the induction visit.
13. A 12-lead ECG will be collected after the participant has been in a supine position for at least 5 minutes and before collecting blood samples. Participants having same-day screening and induction visits are not required to repeat the ECG for the induction visit.
14. The TM buprenorphine is to be administered or dispensed at the discretion of the Investigator, per the applicable product labelling information.
[redacted]
16. Assessments will be completed on Day 1 prior to RBP-6000 injection once it has been determined that the participant will proceed with receiving the injection (i.e., meets RBP-6000 dosing criteria in Section 4.1.2.2).
[redacted]
18. Injection site will be evaluated and any injection site reactions or infections will be recorded as AEs.
19. Participants will receive counselling during the treatment period.

22.4 Schedule of Events – Week 1 Day 2 to Week 16 – All On-site Visits

	Visit Name	W1 D2	W2 D8	W2 D9	W3 D15	W4 D22	W5 D29	W6 D36	W7 D43	W8 D50	W9 D57	W10 D64	W12 D78	W14 D92	W16 D106
	RBP-6000 Injection Number		2					3				4		5	
	Window (days)	+1	+4	+1	-2/+4	-2/+4	-2/+4	-2/+4	-2/+4	-2/+4	-2/+4	-2/+4	-7/+7	-2/+4	-7/+7
	Telephone follow up	X[1]		X[1]											
nts	Urine Pregnancy Test[2]		X					X		X		X		X	
	UDS[3]		X		X	X	X	X	X	X	X	X	X[4]	X	X[4]
	Self-reports/TLFB[5]		X		X	X	X	X	X	X	X	X	X[4]	X	X[4]
[redacted]															
5000 As	Vital Signs[7]		X		X	X	X	X				X		X	
	12-Lead ECG[8]		X			X		X							
[redacted]															
	Weight/BMI[11]		X					X				X		X	
	AE Assessment and Concomitant Medications[12]	◄													►
	Double-blind Randomisation[13]							**X**							
	RBP-6000 Administration[14]		X					X				X		X	
	Injection Site Evaluation[15]		X					X				X		X	
	Counselling [16]	◄													►

AE=adverse event; BMI=body mass index; D=day; ECG=electrocardiogram; [redacted]

[redacted] TLFB= TimeLine Follow Back; UDS=urine drug screen; W=week; [redacted]

1. Participants will be followed up via telephone the day after the first and second RBP-6000 injections.
2. Required for female participants of child-bearing potential only. Urine pregnancy test must be performed prior to RBP-6000 dosing. Participants with positive pregnancy tests (urine test confirmed by serum test) will be discontinued.
3. Qualitative on-site dipstick to be performed on Week 6 only to stratify the randomisation. The UDS at all other visits will be performed by central lab.
4. Visits between Injections 4 to 10 are to be scheduled by the Investigator at random (2 weeks±7 days post each injection) to complete a UDS and TLFB only. Site may perform TLFB as an interview over the phone within 24 hours of UDS collection.
5. Details participants daily drug use for each of the past 7 days, in addition to capturing the main route of use (and more specifically, if an injectable route was used), and number of times used.

[redacted]

7. Includes systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature after the participant has been in a sitting position for at least 3 minutes.
8. A 12-lead ECG will be collected after the participant has been in a supine position for at least 5 minutes and before collecting blood samples. On injection days, ECG will be completed ≤60 minutes prior to RBP-6000 administration.

[redacted]

11. Weight to be collected at any time during the visit. Height will be measured only at the Screening Visit. Body mass index will be calculated within the database using weight and height.
12. Includes a review of any previous (taken since the last visit) and ongoing medications, including over-the-counter medications and herbal supplements.
13. Participants will be randomised to either 100-mg or 300-mg RBP-6000 maintenance dose. Note that Week 6 UDS result for opioids (negative or positive) must be available prior to randomisation.
14. RBP-6000 will be administered by an unblinded staff member, see Section 9.5.
15. Previous injection sites will be evaluated for evidence of attempted removal. If there is any evidence of attempted depot removal, the Investigator must discuss with the medical monitor about whether the participant should remain in the study. Current injection site will be also assessed before the participant leaves the site and any injection site reactions or infections will be recorded as AEs.
16. Participants will receive counselling during the treatment period.

22.5 Schedule of Events – Week 18 to 36 – All On-site Visits

	Visit Name	W18 D120	W20 D134	W22 D148	W24 D162	W26 D176	W28 D190	W30 D204	W32 D218	W34 D232	W36 D246
	RBP-6000 Injection Number	6		7		8		9		10	
	Window (days)	-2/+4	-7/+7	-2/+4	-7/+7	-2/+4	-7/+7	-2/+4	-7/+7	-2/+4	-2/+4
ents	Urine Pregnancy Test[1]	X		X		X		X		X	
	UDS[2]	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X	X
	Self-reports/TLFB[4]	X	X[3]	X	X[3]	X	X[3]	X	X[3]	X	X
[redacted]											
000	Vital Signs[6]	X		X		X		X		X	X
[redacted]											
	Weight/BMI[9]	X		X		X		X		X	X
	AE Assessment and Concomitant Medications[10]	←									→
	RBP-6000 Administration[11]	X		X		X		X		X	
	Injection Site Evaluation[12]	X		X		X		X		X	X
	Counselling [13]	X									

AE=adverse event; BMI=body mass index; COWS=Clinical Opiate Withdrawal Scale; D=day; ECG=electrocardiogram; [redacted] TLFB=TimeLine Follow Back; UDS=urine drug screen; W=week; [redacted]

1. Required for female participants of child-bearing potential only. Urine pregnancy test must be performed prior to RBP-6000 dosing. Participants with positive pregnancy tests (urine test confirmed by serum test) will be discontinued. Pregnant participants who have already received their final (10th) RBP-6000 injection may continue to complete the study.
2. The UDS will be performed by central laboratory.
3. Visits between Injections 4 to 10 are to be scheduled by the Investigator at random (2 weeks±7 days post each injection) to complete a UDS and TLFB only. Site may perform TLFB as an interview over the phone within 24 hours of UDS collection
4. Details participants daily drug use for each of the past 7 days, in addition to capturing the main route of use (and more specifically if an injectable route was used), and number of times used.

[redacted]

6. Includes systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature after the participant has been in a sitting position for at least 3 minutes.

[redacted]

9. Weight to be collected at any time during the visit. Height will be measured only at the Screening Visit. Body mass index will be calculated within the database using weight and height.
10. Includes a review of any previous (taken since the last visit) and ongoing medications, including over-the-counter medications and herbal supplements.
11. RBP-6000 will be administered by an unblinded staff member, see Section 9.5.
12. Previous injection sites will be evaluated for evidence of attempted removal. If there is any evidence of attempted depot removal, the Investigator must discuss with the medical monitor about whether the participant should remain in the study. Current injection site will be also assessed before the participant leaves the site and any injection site reactions or infections will be recorded as AEs.
13. Participants will receive counselling during the treatment period.

22.6 Schedule of Events – Week 38 to Week 40 End of Study and Early Termination

Visit Name	EOT W38 D260	ET (RBP-6000)	ET[1] (TM BUP)	EOS[2] W40 D274
Visit Type	**On-site**	**On-site**	**Phone Call**	**Phone Call**
Window (days)	**-2/+4**		**24-72 hr Post-TM BUP**	**-2/+4**
Urine Pregnancy Test[3]	X	X		
UDS[4]	X	X		
Self-reports/TLFB[5]	X	X		
[redacted]				
Weight/BMI[7]	X	X		
Vital Signs[8]	X	X		
12-Lead ECG[9]	X	X		
Serum Chemistry and Haematology, Urinalysis	X	X		
HIV-1/HIV-2, Hep B, Hep C Antibody[10]	X	X		
[redacted]				
AE Assessment and Concomitant Medications[12]	←	—	—	→
[redacted]				
Injection Site Evaluation[13]	X	X		
Physical Examination[14]	X	X		
Counselling[15]	X	X		

AE=adverse event; BMI=body mass index; BUP= buprenorphine; COWS=Clinical Opiate Withdrawal Scale; D=day; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; ET=Early Termination; [redacted] Hep=hepatitis; HIV=human immunodeficiency virus; [redacted]

[redacted] TLFB= TimeLine Follow Back; UDS=urine drug screen; W=week; [redacted]

1. Participants who discontinue from the study and have been administered TM buprenorphine but have not been dosed with RBP-6000 and have ongoing AEs will be contacted by telephone 24-72 hours after the last TM buprenorphine dose to assess any ongoing AEs and concomitant medication associated with those ongoing AEs use.
2. Participants will be contacted by telephone to assess any AEs that were ongoing at the EOT/last visit. Participants do not need to return to the site unless deemed medically necessary by an Investigator.
3. Required for female participants of child-bearing potential only.
4. The UDS will be performed by central lab.
5. Details participants daily drug use for each of the past 7 days, in addition to capturing the main route of use (and more specifically, if an injectable route was used).

[redacted]

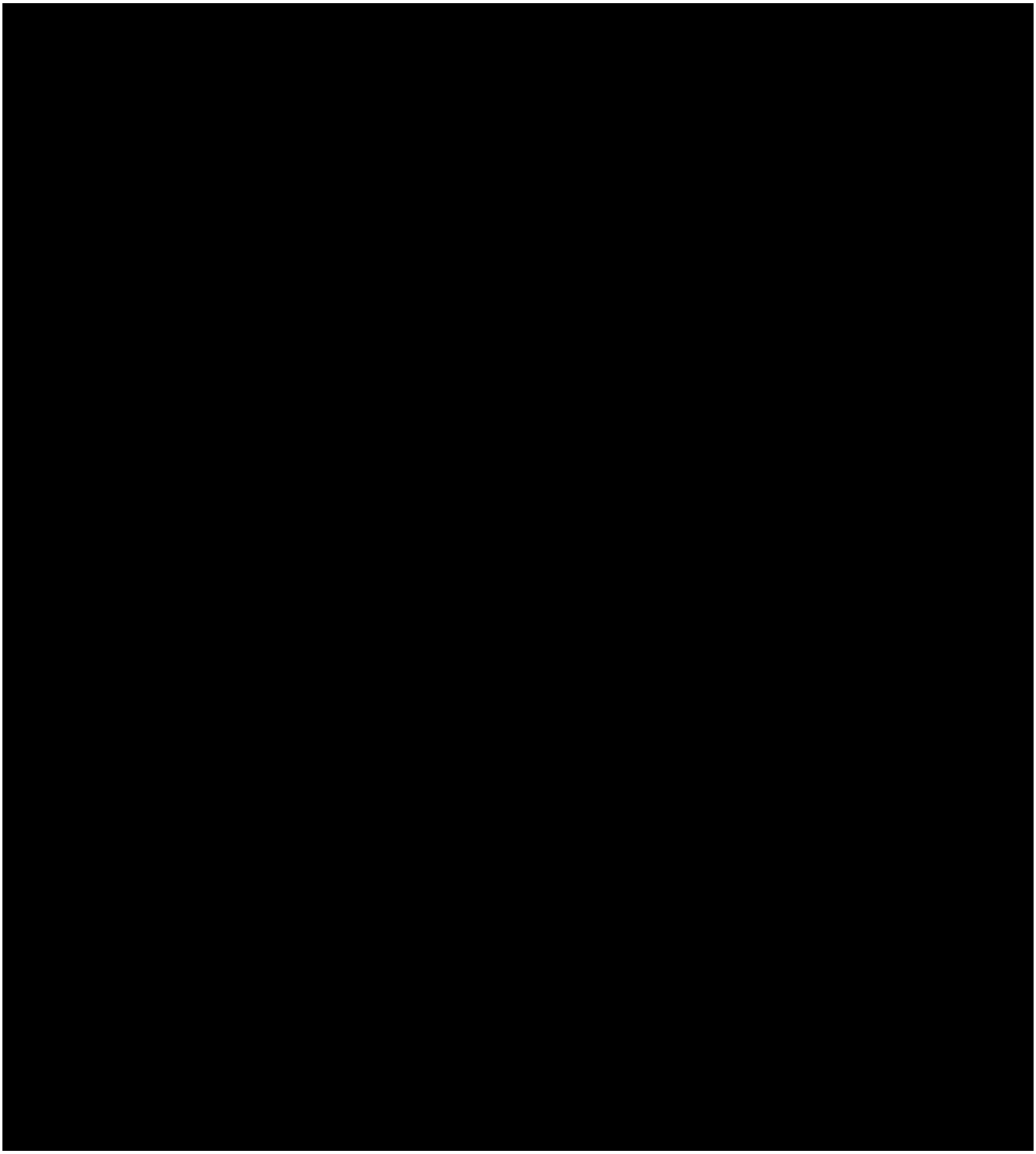
7. Weight to be collected at any time during the visit. Height will be measured only at the Screening Visit. Body mass index will be calculated within the database using weight and height.
8. Includes systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature after the participant has been in a sitting position for at least 3 minutes.
9. A 12-lead ECG will be collected after the participant has been in a supine position for at least 5 minutes and before collecting blood samples.
10. The HIV-1/HIV-2, Hep B and Hep C antibody testing is to be performed at EOT/ET only if the participant was negative at Screening.

[redacted]

12. Includes a review of any previous (taken since the last visit) and ongoing medications, including over-the-counter medications and herbal supplements.
13. Previous injection sites will be evaluated for evidence of attempted removal. If there is any evidence of attempted depot removal, the Investigator must inform the medical monitor. Any injection site reactions or infections will be recorded as AEs.
14. Complete physical examination to include an assessment of general appearance, skin and extremities, head and neck, lymph nodes, eyes, ears, nose, throat, thyroid, neurological system, lungs, cardiovascular system and abdomen (liver and spleen). The examination will not include a breast, pelvic or rectal exam, unless clinically indicated.
15. Participants will receive counselling during the treatment period.

22.7 Liver Safety

The following should occur if a participant meets any of the Liver Chemistry Stopping Criteria as outlined in Section 6.7.3 of the protocol:



Please refer to the FDA Guidance for Industry *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* (FDA 2009). for standard of care for the evaluation of aetiology in participants who meet any of the above criteria.

22.8 Morphine Dose Analgesic Equivalence Table

It should be noted that below conversions are only intended to convert an IV administered opioid to morphine equivalents based on analgesic dose ranges (Laird 2016). For opioids administered by other routes, see footnotes to table below.

Opioid	IV (mg)
Buprenorphine	41.7*
Codeine	1250
Heroin	500
Hydrocodone	NA*
Hydromorphone	187.5
Meperidine	9375
Morphine	1250
Oxycodone	NA*
Oxymorphone	125
Tapentadol	NA*
Tramadol	NA*

IV=intravenous
Notes: Heroin is generally 2.5-fold more potent than morphine, i.e., 1250 mg IV morphine is equivalent to 500 mg IV heroin. For smoking/nasal use, assume a 50% bioavailability compared to IV (Rook 2006).
*For oral/transmucosal preparations with even poorer bioavailability, it is considered impractical to achieve exposures equivalent to 500 mg IV heroin. For example, transmucosal buprenorphine 139 mg x 12 (relative heroin potency) x 0.3 (bioavailability) = 500 mg IV heroin equivalents.
Source: National Cancer Institute 2020, Chou 2009

22.9 Open-Label Induction Sub-study

1. SUB-STUDY INTRODUCTION AND RATIONALE

See main protocol Section 1.2.2 for the Open-label Induction Sub-study rationale.

2. SUB-STUDY OBJECTIVES

The primary objective of this sub-study is to compare treatment retention of participants following rapid induction or SoC induction onto RBP-6000.

The secondary objective of this sub-study is to evaluate the safety and tolerability of RBP-6000 in participants during the Open-label Induction Sub-study.

[redacted]

3. SUB-STUDY ENDPOINTS

The primary endpoint of this sub-study is treatment retention at Injection 2 defined as the proportion of participants receiving Injection 2 at the Week 2 visit among those who received at least 1 dose of TM buprenorphine for induction and did not demonstrate idiosyncratic response to the first dose of TM buprenorphine. Participants who discontinue treatment due to not meeting Inclusion/Exclusion criteria will be excluded.

The secondary endpoints of this sub-study are the following:

- time to treatment discontinuation from the first dose of TM buprenorphine used for induction during the Open-label Treatment Period (OLTP) defined as the number of days from the first dose of TM buprenorphine until the last scheduled visit observed during the OLTP. Participants receiving the third RBP-6000 injection (i.e., the first randomised injection) will be censored administratively at the end of the OLTP; otherwise participants will be viewed as having discontinued treatment at their last scheduled visit observed during the OLTP. Participants discontinued due to idiosyncratic response to the first dose of TM buprenorphine or not met meeting Inclusion/Exclusion criteria will not be included.

- adverse events up to Injection 2, and between Injections 2 and 3

[redacted]

4. SUB-STUDY PLAN

Study plan activities that will provide data to be analysed as part of the Open-label Induction Sub-Study are described in main protocol Section 4.1.1 (Screening and Induction Qualification), 4.1.2 (Induction) and 4.1.3 (Second Dose of RBP-6000).

5. SUB-STUDY POPULATION

In the main study, it is planned for approximately 390 participants to be randomised immediately prior to their third injection. Assuming a minimal 20% discontinuation rate during the OLTP prior to the third injection of RBP-6000, it is estimated that at least 489 participants will need to be randomised to the 2 induction arms (Rapid Induction vs SoC) in the sub-study to achieve the planned number of participants (n=390) in the main study.

For this sub-study, 2 planned interim analyses may be performed when at least 120 and at least 240 participants (respectively), who received TM buprenorphine treatment, have either received Injection 3 or discontinued prior to Injection 3.

6. SUB-STUDY CONDUCT

6.1. Sub-study Screening

All participants are considered screened for both the main study and sub-study once written informed consent is obtained; a participant identification number is then assigned. There is no separate informed consent for this sub-study.

6.2. Sub-study Enrolment

A participant will be considered enrolled in the sub-study if he/she gives informed consent and is randomised in the sub-study.

7. DESCRIPTION OF SUB-STUDY PROCEDURES

Assessments to be analysed for the Open-label Induction Sub-study will be collected as described in the main protocol.

8. SUB-STUDY STATISTICS

8.1. General Procedures

8.1.1. Analysis Conduct

A SAP will be prepared after the protocol is approved and will be signed off before database lock occurs. The SAP will provide further details regarding analysis. Additional unplanned analyses may be required after all planned analyses have been completed. Any deviations from the analyses described below will be outlined in the SAP. Any unplanned analyses will be clearly identified in the clinical study report.

The interim and final analyses (Section 8.10) will be performed following lock of the CRF data required for each analysis.

8.1.2. Analysis Conventions

Continuous variables will be summarised using descriptive statistics such as mean, SD, coefficient of variation, geometric mean, median, minimum and maximum. Categorical variables will be reported as frequency counts (including number missing) and the percentage of participants in corresponding categories. Individual participant data will be presented by participant in data listings. Data listings will include all data collected.

8.1.3. Groups for Comparison

Data will be summarised and comparisons will be made (where applicable) by RBP-6000 induction arm: rapid induction and SoC induction.

8.2. Statistical Hypothesis

For the primary endpoint (treatment retention at Injection 2), the null hypothesis H_0 is retention rate of rapid induction – SoC induction
$\leq$ -10% (non-inferiority margin of 10%), the alternative hypothesis H_A is retention rate of rapid induction – SoC induction > -10%. The criterion for success (i.e., demonstrating non-inferiority) at an interim analysis (IA) or final analysis is based on the posterior probability of retention rate difference (rapid – SoC) > -10%. The non-inferiority of rapid induction to the SoC induction will be declared if the posterior probability is higher than

96%. The 96% critical value is chosen so that the overall 1-sided Type I error is less than 10%.

8.3. Sample Size and Power for Sub-study

The sample size for the sub-study is based on the required sample size for the main study and the assumed premature discontinuation rate in the sub-study, as the sub-study is an integral part of the main study. Approximately 489 participants will be randomised in a 2:1 ratio to rapid induction or SoC induction arms. Under the assumption of 70% retention rate at Injection 2 for both arms and with 2 planned IAs at 120 and 240 participants, a total of 489 participants will provide 77.2% power to conclude non-inferiority (NI) of rapid induction to SoC induction under 10% NI margin. Sub-study Table 1 provides cumulative power at the 2 planned IAs and the final analysis under different assumptions of retention rate at Injection 2, with scenarios of same retention for both arms or greater retention rate for rapid induction. The assumption about the possible retention rate at Injection 2 was based on the retention rates observed in the 2 previous Phase 3 studies. Among the OUD participants who initiated SoC induction, about 65.7% (or 72.1%) received their second RBP-6000 injection. For injection route users, the retention rate was about 64.4% (or 70.1%).

Sub-study Table 1 Cumulative Power at 2 Planned Interim Analyses and Final Analysis Under Different Assumptions of Retention Rate at Injection 2

	Assumptions of Retention Rate at Injection 2				
Analysis	**$P_{SoC}=P_R=0.65$**	**$P_{SoC}=P_R=0.70$**	**$P_{SoC}=P_R=0.75$**	**$P_{SoC}=P_R=0.80$**	**$P_{SoC}=P_R=0.85$**
IA at n=120	0.277	0.294	0.324	0.369	0.449
IA at n=240	0.489	0.517	0.564	0.627	0.723
FA at n=489	0.742	0.772	0.817	0.869	0.932
	$P_{SoC}=0.65$ $P_R=0.70$	**$P_{SoC}=0.7$ $P_R=0.75$**	**$P_{SoC}=0.75$ $P_R=0.80$**	**$P_{SoC}=0.80$ $P_R=0.85$**	**$P_{SoC}=0.85$ $P_R=0.90$**
IA at n=120	0.498	0.538	0.598	0.679	0.804
IA at n=240	0.780	0.816	0.867	0.922	0.974
FA at n=489	0.963	0.976	0.988	0.996	>0.999
	$P_{SoC}=0.65$ $P_R=0.75$	**$P_{SoC}=0.70$ $P_R=0.80$**	**$P_{SoC}=0.75$ $P_R=0.85$**	**$P_{SoC}=0.80$ $P_R=0.90$**	**$P_{SoC}=0.85$ $P_R=0.95$**
IA at n=120	0.726	0.781	0.844	0.924	0.988
IA at n=240	0.945	0.968	0.986	0.998	>0.999
FA at n=489	0.998	0.999	>0.999	>0.999	>0.999

FA=Final Analysis; IA=Interim Analysis; P_R=retention rate of rapid induction; P_{SoC}=retention rate of SoC

Induction; SoC=standard of care
A total of 100,000 simulations are performed per scenario.

8.4. Analysis Populations

8.4.1. Sub-study Enrolled Population

The Sub-study Enrolled Population (SEP) will be used for analyses of participant disposition. The SEP will comprise all participants who give informed consent and are randomised to sub-study treatment. The participants will be analysed corresponding to the induction arm to which they were randomised.

8.4.2. Sub-study Full Analysis Set

The Sub-study Full Analysis Set (SFAS) will serve as the primary population for the analysis in this sub-study. The SFAS will comprise all participants who are randomised to sub-study treatment and receive the first dose of TM buprenorphine and do not demonstrate idiosyncratic response to the first dose of TM buprenorphine. The participants will be analysed corresponding to the induction arm they received. For analysis pertaining to treatment retention and time-to-treatment discontinuation, the participants who discontinue treatment due to not meeting Inclusion/Exclusion criteria will be excluded. The analysis population for the IA is defined in Section 8.10.

8.5. Primary Endpoint Analysis: Treatment Retention at Injection 2 (received at Week 2 visit)

Retention rate will be estimated by Bayesian beta-binomial model using non-informative uniform prior, i.e., Beta (1,1), within individual induction arms. The posterior distribution of retention rate difference between the 2 arms will be obtained and utilised to calculate the posterior probability of non-inferiority of the rapid induction to SoC induction using a 10% NI margin or a favourable trend of the rapid induction over the SoC induction. The criterion for success (i.e., demonstrating NI) is based on the posterior probability of retention rate difference (rapid – SoC) greater than -10%. The NI of rapid induction will be declared if the posterior probability is at 96% or greater. If the NI is declared, the posterior possibility for superiority of rapid induction over SoC induction will be evaluated.

8.6. Secondary Endpoint Analysis: Time to Treatment Discontinuation from the First Dose of TM Buprenorphine Induction

The time from the first dose of TM buprenorphine to treatment discontinuation will be presented by induction arm using a Kaplan-Meier (KM) curve within the randomisation strata (UDS fentanyl negative vs. positive at the day of first dose of TM buprenorphine) and for overall. Participants receiving the third RBP-6000 injection (i.e., the first

randomised injection) will be censored administratively at the end of the OLTP. Retention rate (with 95% CI) at specific time point will be estimated using KM product limit method for each induction arm. Hazard ratio (with 95% CI) of RBP-6000 rapid induction to SoC induction will be estimated using a Cox proportional hazard model, with arm as a single covariate, stratified by the randomisation strata.

[redacted]

8.8. Safety Analysis

Safety data will be summarised by induction arm and overall for the analysis period up to Injection 2 and overall only for the analysis period between Injections 2 and 3. Complete details of the safety analyses will be provided in the SAP.

8.8.1. Extent of Exposure

Exposure to TM buprenorphine and RBP-6000 will be summarised by induction arm and overall.

8.8.2. Adverse Events

Adverse events will be coded using MedDRA and grouped by system organ class. For this sub-study, events that occurred after the first induction dose of TM buprenorphine up to Injection 3 will be listed and summarised.

Events will be summarised with frequency and percentage, by system organ class and preferred term, by induction arm overall and within individual randomisation stratum and overall up to Injection 2 and overall only between Injections 2 and 3. Separate summaries will be provided for all TEAEs, drug-related TEAEs, TEAEs by severity, serious TEAEs, TEAEs leading to discontinuation of study treatment, TEAEs of special interest (including exacerbated withdrawal symptoms) and injection site reaction TEAEs.

The incidence of deaths will also be reported and the primary causes of death summarised.

8.9. Other Analyses

Additional details of these other analyses will be provided in the SAP.

Demographic and disease characteristics at Screening (e.g., sex, race, age, weight, and BMI) will be summarised for the SFAS overall and by induction arm using descriptive statistics.

Results of UDS and TLFB on the first induction day will be summarised by substance for the SFAS overall and by induction arm, for the UDS and TLFB assessments separately and combined across both assessments using descriptive statistics.

[redacted]

The number and percentage of participants taking concomitant medications (any medication and medications to treat withdrawal symptoms) during the time period from the first dose of TM buprenorphine through Injection 2 will be summarised for the SFAS overall and by induction arm overall and within individual randomisation stratum using descriptive statistics.

The COWS scores at each timepoint and visit during the OLTP will be summarised overall, and by induction arm overall and within individual randomisation stratum using descriptive statistics; the difference in group mean will be estimated with a 95% CI for each timepoint and visit.

8.10. Interim Analysis

As the sub-study is sponsor open-label and maintaining the treatment blind is not a factor in sub-study integrity, study personnel will perform the interim analysis(es). Two interim analyses will be performed when at least 120 and at least 240 participants (respectively) treated with TM buprenorphine, who have either received Injection 3 or discontinued prior to Injection 3, to allow early declaration of non-inferiority of rapid induction to SoC induction with respect to treatment retention at Injection 2. At each IA, the criterion of NI is the posterior probability of retention rate difference (rapid – SoC) > -10% being 96% or greater.

If NI is declared at the IA, the results will be shared within Indivior.

The final analysis for the sub-study will occur after all participants have enrolled and completed the sub-study. The sub-study will be considered positive for the primary endpoint, if the posterior probability of retention rate difference (rapid – SoC) > -10% is 96% or greater. If the NI of rapid induction to SoC induction is concluded, the posterior possibility for superiority of rapid induction over SoC induction will be evaluated.

A 96% critical value at each IA and the final analysis is chosen to provide overall 1-sided Type I error less than 10%. Sub-study Table 2 shows 1-sided Type I error at each IA, final analysis and overall, for 5 null hypothesis scenarios for 10% NI margin where the retention rate of rapid induction is truly 10% less than control.

Sub-study Table 2 1-sided Type I Error at Each IA, Final Analysis and Overall, Under Different Null Scenarios for 10% Non-inferiority Margin

	Assumptions of Retention Rate at Injection 2				
Analysis	**P_{SoC}=0.65 P_R=0.55**	**P_{SoC}=0.70 P_R=0.60**	**P_{SoC}=0.75 P_R=0.65**	**P_{SoC}=0.80 P_R=0.70**	**P_{SoC}=0.85 P_R=0.75**
IA at n=120	0.0426	0.0439	0.0446	0.0462	0.0467
IA at n=240	0.0258	0.0267	0.0258	0.0263	0.0276
FA at n=489	0.0232	0.0234	0.0237	0.0235	0.0235
Overall	0.0916	0.0941	0.0941	0.0959	0.0978

FA=Final Analysis; IA=Interim Analysis; P_R=retention rate of rapid induction; P_{SoC}=retention rate of SoC induction; SoC=standard of care
A total of 100,000 simulations are performed per scenario.

For the interim analysis(es), the analysis population will be defined as the first 120/240 participants (at minimum) who are randomised and receive TM buprenorphine, based on the date of the first dose of TM buprenorphine. Participants will be included in the treatment group (rapid induction or SoC induction) to which they actually received.

If NI is declared at the first IA, then the second IA might not be performed. The final analysis will be performed irrespective of the number of IAs.

8.11. Handling of Missing Data

Observed data will be used for the analysis with no imputation of missing values.

For graphical and summary purposes, buprenorphine plasma concentration values below the limit of quantification will be set to zero.

The handling of spurious data will be documented in the study report.