Title: Virginia Opioid overdose Treatment InitiatiVE (VOTIVE)

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Clinical Study Protocol

Protocol Title:	Virginia Opioid overdose Treatment InitiatiVE (VOTIVE)
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Protocol Revision Date:	October 23, 2020
Protocol Version:	9.0

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I have read the protocol, including all appendices, and I agree that it contains all 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 Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about the IMP and appropriate information throughout the study. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Signed:_____ Date:_____

F. Gerard Moeller, MD 23-October-2020
Director, Institute for Drug and Alcohol Studies
Virginia Commonwealth University

STUDY SYNOPSIS

Protocol Title:
Virginia Opioid overdose Treatment InitiatiVE (VOTIVE)
Indivior Inc. Reference Number: INDV-6000-304

Rationale:
Individuals with opioid use disorder (OUD) who overdose (OD) on opioids have a high risk of repeat opioid OD. At the Virginia Commonwealth University (VCU) Medical Center, emergency department (ED) data between 2015 and the end of 2017 indicate that, on average, 27% of individuals seen for an index opioid OD in the ED had a second event (OD or death due to opioid OD). Seventy percent of these events occurred within the first 6 months following the index episode with the majority occurring in the first 2 months post initial OD. Most likely due to the prevalence of fentanyl and fentanyl derivatives in heroin, the risk of fatality with opioid OD has risen exponentially in the United States (US) over the last several years (Mercado 2014).

Treatment of OUD patients at high risk of OD (such as when released from incarceration), with methadone or buprenorphine reduces the risk of OD index cases by up to 85% (Marsden 2017). This study will assess whether OUD patients treated with SUBLOCADE™ (buprenorphine extended-release injection for subcutaneous use) in the ED, inpatient unit, or at the clinic within 7 days (168 h) of overdose after receiving a test dose of SUBOXONE® (buprenorphine and naloxone) following OD reversal with an opioid antagonist reduces subsequent opioid OD events (repeat OD and/or repeat OD with fatality) as compared to a historical control cohort and concurrent controls who decline treatment participation. The study will also provide data on feasibility of initiation of SUBLOCADE within 7 days (168 h) of an overdose and data on subsequent outpatient treatment engagement.

Target Population:

Adults with moderate to severe OUD (as defined by DSM-5 criteria) following an opioid OD, received treatment with an opioid antagonist, and are clinically stable for a screening interview.

Number of Subjects: 100

Duration of Treatment:
The total duration of study participation will be approximately 7 months. Subjects will receive treatment for approximately 6 months with an End of Treatment (EOT) visit at 7 months post treatment initiation.

Objective(s):
The primary objective of this study is:

- Determine the effect of SUBLOCADE treatment in the ED, inpatient unit or in the clinic within 7 days (168 h) after opioid OD on repeat OD and death compared to a historical control group and concurrent controls who decline treatment participation.

The key secondary objective of this study is:

- Determine effect of SUBLOCADE administered in the ED, inpatient unit or in the clinic within 7 days (168 h) after OD on treatment engagement at 3 months and 6 months.

The exploratory objectives of this study are:

- To determine the effect of SUBLOCADE administered in the ED, inpatient unit or in the clinic within 7 days (168 h) of opioid OD followed by SUBLOCADE in the clinic on opioid craving.
- To determine the efficacy of SUBLOCADE that has been administered in the ED, inpatient unit or at the clinic within 7 days (168 h) of opioid OD followed by SUBLOCADE in the outpatient clinic on opioid use as determined by Urine Drug Screen (UDS).
- To evaluate the effect of SUBLOCADE administered within 7 days (168 h) of an opioid OD followed by SUBLOCADE in the clinic on decision making using a delay discounting task and a brief opioid demand measure to measure craving valuation (hypothetical maximum price participants would be willing to pay for access to opioid, assessing craving/valuation).
- To evaluate the association between participant genetic polymorphisms and subjects with history of OD in subjects that consent to the PGx sub-study.
- To evaluate the relationship between genetics/behavioural laboratory measures of decision making and treatment outcome, including repeat OD in subjects that consent to the PGx sub-study.
- To determine the relationship between decision making and treatment retention and illicit opioid use.
- To evaluate healthcare resource utilisation associated with either treatment regimen as compared to the historical control (2015-2018) obtained from VCU anonymized health records.
- To assess the impact of SUBLOCADE administered in the ED, inpatient unit or within 7 days (168 h) of an opioid OD followed by administration of SUBLOCADE in the clinic on treatment effectiveness as measured by Treatment Effectiveness Assessment (TEA), on medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ), and on employment, presentism and absenteeism as assessed by the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP).

Study Design:

This is a Phase 3b, open-label study in patients who are treated for an opioid OD and receive treatment with an opioid antagonist. The study is designed to determine effect of SUBLOCADE on repeat OD and death compared to historical control data.

The study will assess subjects that receive acute administration of SUBOXONE sublingual film followed by SUBLOCADE administration in the 1) ED, 2) inpatient unit or 3) within 7

days (168 h) after OD in an affiliated outpatient treatment clinic combined with 6 months of treatment with SUBLOCADE in the outpatient treatment clinic compared to historical and concurrent control data from VCU electronic health records. The affiliated clinic will agree to see the subject on arrival at the clinic during normal clinic hours.

Subjects will be given the opportunity to participate in an optional pharmacogenetics (PGx) sub-study.

1) Patients presenting to the ED for an opioid OD who received treatment with an opioid antagonist and are considered clinically stable and alert (respiratory rate [RR] ≥ 12, pulse oximetry > 95%, Glasgow Coma Scale [GCS] score of 15), and, who deny recent/regular use of long acting opioids (e.g., methadone) will be approached regarding interest in study participation. Written informed consent will only be obtained if the patient's judgement is intact as determined clinically by the Investigator or a medically qualified sub-investigator or research nurse. This OD will be considered the index OD.

   Participants who meet inclusion/exclusion criteria will be administered 4 mg/1 mg SUBOXONE sublingual film in the ED followed by a 1-hour wait. If the subject displays no allergic/hypersensitivity reaction to SUBOXONE sublingual film after 1 hour, SUBLOCADE (300 mg) will be administered in the ED. Subjects will remain in the ED for 1 hour after the 300 mg SUBLOCADE injection and are clinically stable (respiratory rate [RR] ≥12, pulse oximetry > 95%, Glasgow Coma Scale [GCS] score of 15). A COWS assessment and AEs will be collected prior to SUBLOCADE administration and 1-hour post SUBLOCADE prior to discharge. Participants with initial COWS <8 and who were released from a controlled environment within the past 30 days, will remain in the ED for 2 hours after SUBLOCADE to assess for sedation using the Richmond Agitation-Sedation Scale. Patients will be discharged if RAS is 0 or greater. Patients who present with abnormal vital signs, or sign of sedation will remain in ED until they meet the ED discharge criteria. If participants experience precipitated withdrawal they will be treated symptomatically with medication as described in section 8.4 below.

   Upon ED discharge, patients will be instructed to use over the counter ibuprofen and acetaminophen as needed. They will also be provided with two oral doses of 50 mg of hydroxyzine as ancillary medications if needed in the judgement of the clinician. The subject will receive referral to an outpatient treatment clinic affiliated with the hospital system in which the ED resides.

   Patients presenting to the ED for an opioid OD who received treatment with an opioid antagonist and who are not approached by the study team for enrollment (e.g. OD outside of regular business hours) will be given a referral card by a ED healthcare provider to go to the outpatient clinic for an initial screening visit. Subjects must arrive at the clinic within 7 days (168 h) of OD.

2) Patients presenting to the ED for an opioid OD who received treatment with an opioid antagonist and who are admitted to an inpatient unit will be approached regarding interest in study participation. Patients who are considered clinically stable and alert (respiratory rate [RR] ≥ 12, pulse oximetry >95%, [GCS] score of 15), who deny recent/regular use of long-acting opioids (e.g. methadone) will be approached. Written informed consent will only be obtained if the patient's judgement is intact and there are no other serious underlying medical complications as determined clinically by the Investigator or a medically qualified sub-investigator or research nurse.

   Participants who meet inclusion/exclusion criteria will be administered a 4 mg/1 mg SUBOXONE sublingual film followed by a 1-hour wait. If the participant displays no allergic/hypersensitivity reaction to SUBOXONE sublingual film after 1 hour, SUBLOCADE (300 mg) will be administered on the inpatient unit. Participants will remain in the inpatient unit for 1 hour after the 300 mg SUBLOCADE injection and are clinically stable (respiratory rate [RR] ≥12, pulse oximetry > 95%, Glasgow Coma Scale [GCS] score of 15. A COWS assessment and AEs will be collected prior to SUBLOCADE administration and 1-hour post SUBLOCADE. Participants with initial COWS <8 and who were released from a controlled environment within the past 30 days, will remain in the inpatient unit for 2 hours after 300 mg SUBLOCADE to assess for sedation using the Richmond Agitation-Sedation Scale. Patients will be discharged if RAS is 0 or greater. Patients who present with abnormal vital signs, or sign of sedation will remain in the inpatient unit. If participants experience precipitated withdrawal they will be treated symptomatically with medication as described in section 8.4 below.

   Upon discharge, patients will be instructed to use over the counter ibuprofen and acetaminophen as needed. They will also be provided with two oral doses of 50 mg of hydroxyzine as ancillary medications if needed in the judgement of the clinician. The subject will receive referral to an outpatient treatment clinic affiliated with the hospital system in which the inpatient unit resides.

   Patients presenting to the ED for an opioid OD who received treatment with an opioid antagonist, who are admitted to the inpatient unit and who are not approached by the study team for enrollment(e.g. discharge outside of regular business hours) will be given a referral card to go to the outpatient clinic by a healthcare provider for an initial screening visit. Subjects must arrive at the clinic within 7 days (168 h) of OD.

3) Patients who are seen only by EMS personnel and are given an opioid antagonist for opioid OD but refuse transport to an Emergency Department but would like to be considered for the VOTIVE study will be given a referral card by EMS personnel. Patients who present to the ED or who are admitted to the inpatient unit for an Opioid OD and would like to be considered for the VOTIVE study but who are not approached by the study team (i.e. outside of business hours) will be given a referral card by a healthcare provider. The patient may present to the clinic within 7 days (168 h) of OD event for evaluation and initial screening visit.

In the clinic, subjects will be consented if they express interest in participating in the study. If participants meet study inclusion criteria and none of the exclusion criteria they will be administered 4 mg/1 mg SUBOXONE sublingual film followed by a 1-hour wait. If the subject displays no allergic/hypersensitivity reaction to SUBOXONE sublingual film after 1 hour, SUBLOCADE (300 mg) will be administered in the clinic. Subjects will remain in the clinic for 1 hour after the SUBLOCADE injection and are clinically stable (respiratory rate [RR] ≥12, pulse oximetry > 95%, Glasgow Coma Scale [GCS] score of 15. A COWS assessment and AEs will be collected prior to SUBLOCADE administration and 1-hour post SUBLOCADE prior to discharge. Participants with initial COWS <8 and who were released from a controlled environment within the past 30 days, will remain in the outpatient clinic for 2 hours after 300 mg SUBLOCADE to assess for sedation using the Richmond Agitation-Sedation Scale. Patients will be discharged if RASS is 0 or greater. Patients who present with abnormal vital signs, or sign of sedation will remain in clinic or will be transferred to the ED until they are safe for discharge from the medical facility. If participants experience precipitated withdrawal, they will be treated symptomatically with medication as described in section 8.4 below.

Upon discharge, patients will be instructed to use over the counter ibuprofen and acetaminophen as needed. They will also be provided with two oral doses of 50 mg of hydroxyzine as ancillary medications if needed in the judgement of the clinician.

Once subjects are engaged in care at the treatment clinic, they will continue to receive SUBLOCADE for 6 months. The second 300 mg injection will be administered on Day 8(-0/+4 days) after the first injection, with subsequent 300 mg injections administered at 28-day (-2/+4 days) intervals over approximately 6 months for a total of 7 injections. If necessary, for tolerability, the dose of SUBLOCADE can be reduced to 100 mg. All subjects will receive site standard psychosocial therapy at least weekly during the first 3 months of treatment, and twice monthly thereafter if clinically stable.

All subjects will complete an End of Treatment (EOT) / Early Termination (ET) visit 28 days after their last injection of SUBLOCADE. Within 3 months prior to or at the EOT visit, the Investigator or a medically qualified sub-investigator will discuss the subject's available treatment options and arrange referral. All subjects will receive a safety follow-up telephone call, 30 days after their EOT/ET visit to assess AEs, SAEs, pregnancy status (if applicable) and concomitant medications. Subjects who decline to continue in medication assisted treatment (MAT) will receive monthly safety follow-up phone calls for an additional 5 months (6 months total) to assess SAEs, pregnancy status (if applicable) and concomitant medications.

Primary Endpoint(s):

The primary endpoint of this study is:

- Time to repeat OD or opioid-related death. Repeat OD or opioid-related death will be measured from electronic medical records and state death registries.
- Additional comparisons on repeat OD and death rates will be made to concurrent patients who decline to participate in the SUBLOCADE injection.

Secondary Endpoint(s):

The key secondary endpoint of the study is:

- Treatment engagement as measured by attending the outpatient clinic and receiving subsequent buprenorphine treatment at 3 and 6 months.

The secondary endpoints of this study are:

- Numbers and percent of subjects in treatment at 3 and 6 months after opioid OD.

Exploratory Endpoints:

The exploratory endpoints of this study are:

- Opioid craving in subjects as measured by Craving Visual Analog Scale (VAS) scores.
- Illicit opioid use as measured by urine drug screen (UDS) results.
- Genetic predictors of treatment response and OD.
- Predictability of treatment response based on impulse control as measured by decision making in the delay discounting task, and opioid cravings/valuation as measured by the brief opioid demand task.
- Healthcare resource utilisation as compared to the historical control (2015-2018) obtained from VCU anonymized health records.
- Treatment effectiveness as measured by Treatment Effectiveness Assessment (TEA), medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ), and employment, presentism and absenteeism as assessed by the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP).

Safety Assessments:

Safety assessments include the proportion of subjects with AEs of the following types at any time during the treatment period: at least 1 AE, a drug-related AE, an SAE, a serious and drug-related AE, or an AE leading to treatment discontinuation.

Additional safety assessments include laboratory assessments, brief physical examinations, vital signs and concomitant medications. Worsening or initiation of withdrawal symptoms, based on observation and subject self-report, will be evaluated during Visit 1 (ED, inpatient unit or Clinic) after SUBOXONE and SUBLOCADE. If participants experience precipitated withdrawal, they will be treated symptomatically with medication as described in section 8.4 below.

Health Economics and Outcomes Assessments:

Health economics and outcomes assessments include the include Healthcare Resource Utilization questionnaire (HCRU), the Treatment Effectiveness Assessment (TEA), the Medication Satisfaction Questionnaire (MSQ), and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP).

Statistical Methods:

Prospective Analyses for the Primary and Key Secondary Endpoints:

The primary endpoint, numbers of subjects who have a repeat OD or OD related death will be analysed using a Cox proportional hazards model controlling for route of administration and comorbid substance use disorder compared to a historical control group and to concurrent subjects who decline SUBLOCADE treatment.

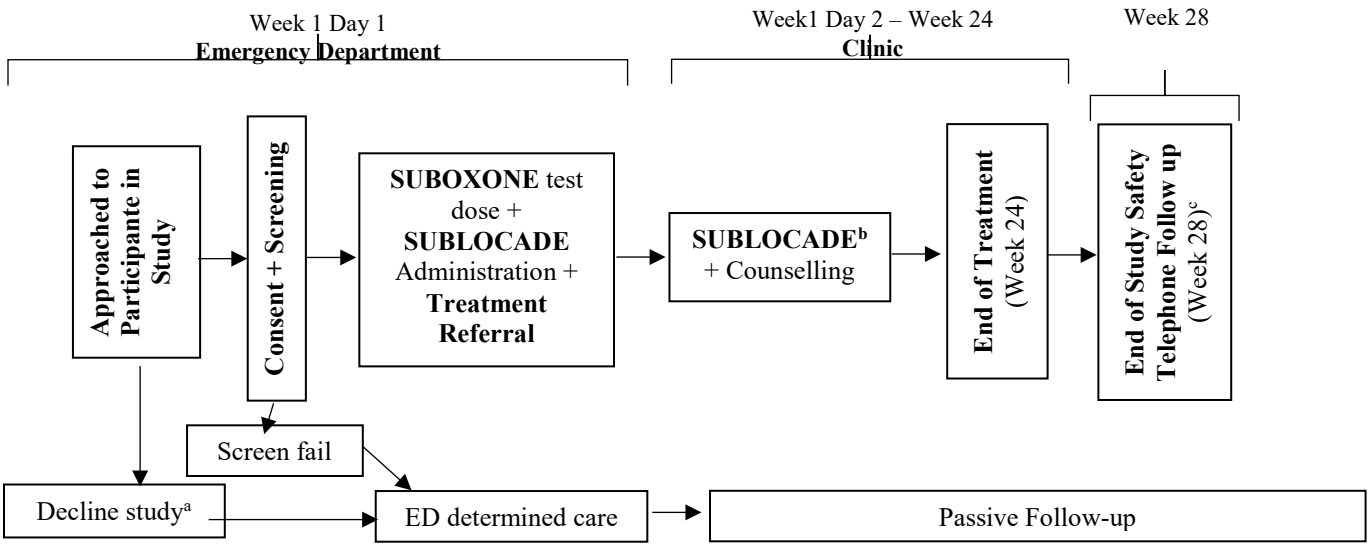
The secondary endpoint, treatment engagement as measured by attending the outpatient clinic and receiving subsequent buprenorphine treatment at 3 and 6 months will be analysed using a Cox proportional hazards model comparing patients with primarily intravenous vs non-intravenous routes of opioid use.

Planned Analyses:

The primary analysis will be performed on the primary and key secondary endpoints after all subjects have been enrolled and completed the end of treatment visit. An enrolled subject is defined as a subject who has received at least one dose of SUBLOCADE.

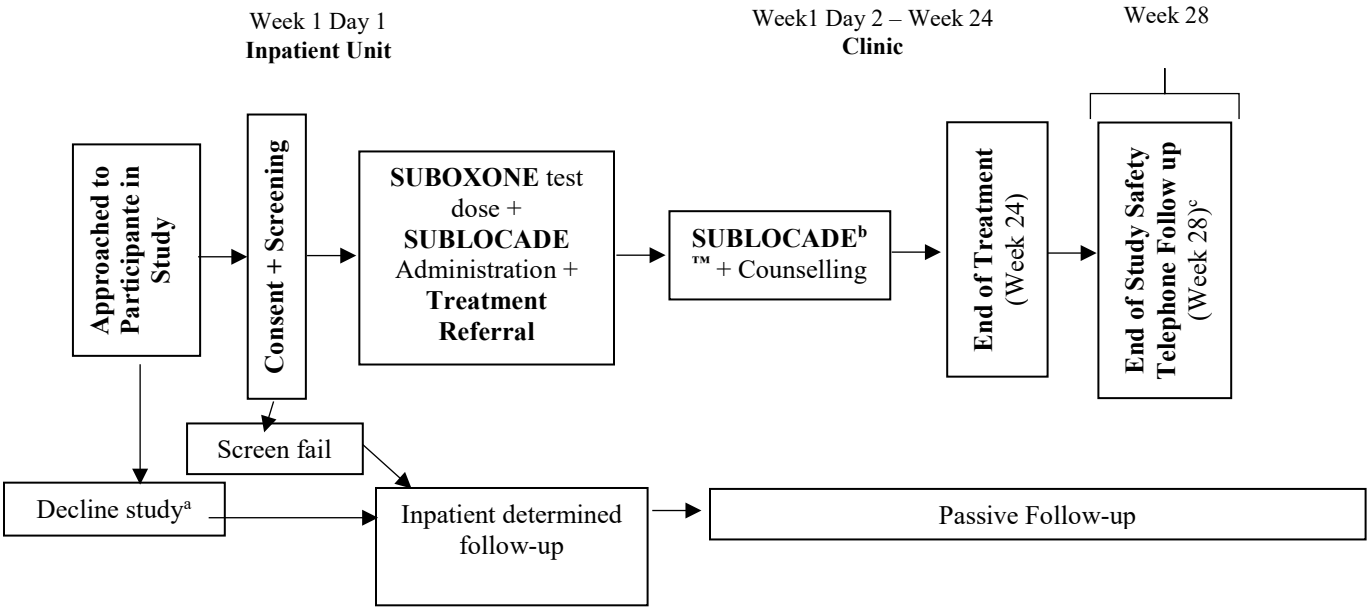
STUDY SCHEMATIC

Figure 1 Study Schematic for SUBLOCADE Initiated in Emergency Department



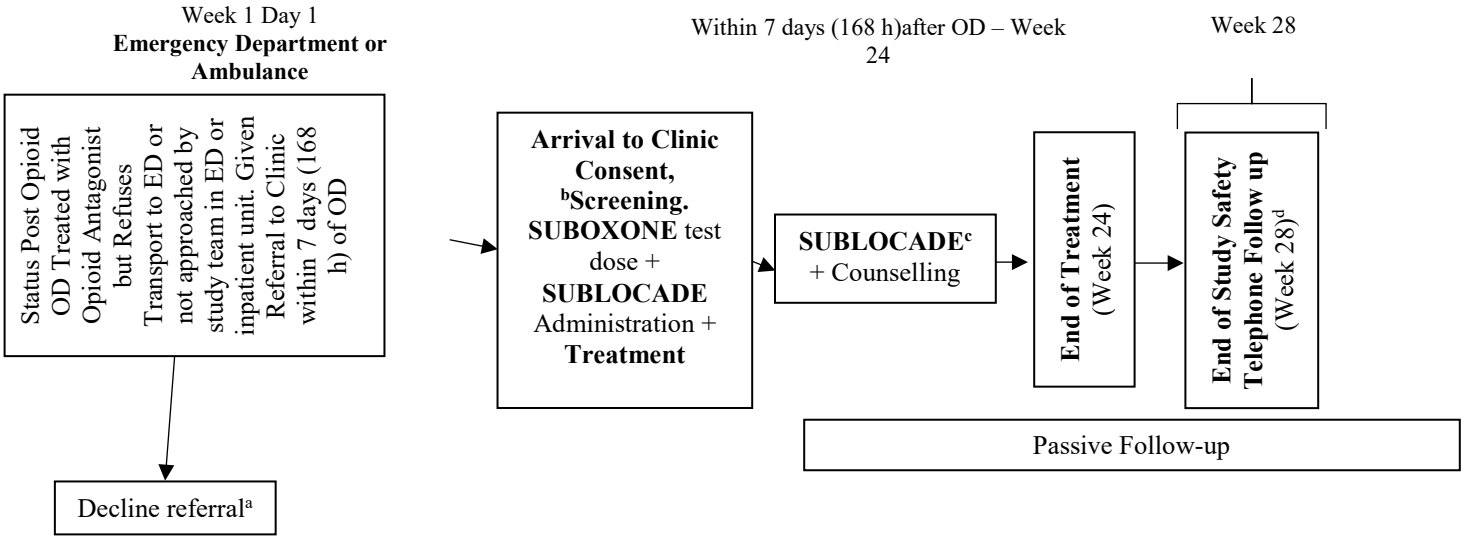
a. Participants who decline to be enrolled in the study will receive care as determined by the ED physicians and continue to be passively followed for 24 weeks. Passive follow-up will include tracking for treatment initiation and engagement and repeat OD via anonymized medical records and tracking for death using state death registries.
b. Injection 2 will be 300 mg and will occur on Day 8 (-0 /+4 days); Injections 3-7 will remain 300 mg (or 100 mg if unable to tolerate 300 mg as determined by study investigator) administered at 28-day (-2/+4 days) intervals.
c. Intervention subjects will receive a safety follow-up telephone call 30 days after their EOT/ET visit to assess AEs, SAEs, pregnancy status (if applicable) and concomitant medications. Subjects who decline to continue in MAT will receive monthly safety follow-up phone calls for an additional 5 months (6 months total) to assess SAEs, pregnancy status (if applicable) and concomitant medications.

Figure 2 Study Schematic for SUBLOCADE Initiated in Inpatient Unit



a. Participants who decline to be enrolled in the study will receive follow-up care as determined by the inpatient unit physicians and continue to be passively followed for 24 weeks. Passive follow-up will include tracking for treatment initiation and engagement and repeat OD via anonymized medical records and tracking for death using state death registries.
b. Injection 2 will be 300 mg and will occur on Day 8 (-0/+ 4); Injections 3-7 will remain 300 mg (or 100 mg if unable to tolerate 300 mg as determined by study investigator) administered at 28-day (-2/+ 4 days) intervals.
c. Intervention subjects will receive a safety follow-up telephone call 30 days after their EOT/ET visit to assess AEs, SAEs, pregnancy status (if applicable) and concomitant medications. Subjects who decline to continue in MAT will receive monthly safety follow-up phone calls for an additional 5 months (6 months total) to assess SAEs, pregnancy status (if applicable) and concomitant medications.

Figure 3 Study Schematic for Initial Dose of SUBLOCADE in Clinic



a. Participants who decline to be enrolled in the study will receive care as determined by the ED physicians and continue to be passively followed for 24 weeks. Passive follow-up will include tracking for treatment initiation and engagement and repeat OD via anonymized medical records and tracking for death using state death registries.
b. Consent and screening at the clinic will include all procedures that take place in the ED for participants who are enrolled in the ED.
c. Injection 2 will be 300 mg and will occur on Day 8 (-0 /+4 days); Injections 3-7 will remain 300 mg (or 100 mg if unable to tolerate 300 mg as determined by study investigator) administered at 28-day (-2/+ 4days) intervals.
d. Intervention subjects will receive a safety follow-up telephone call 30 days after their EOT/ET visit to assess AEs, SAEs, pregnancy status (if applicable) and concomitant medications. Subjects who decline to continue in MAT will receive monthly safety follow-up phone calls for an additional 5 months (6 months total) to assess SAEs, pregnancy status (if applicable) and concomitant medications.

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List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUD	Alcohol Use Disorder
BMI	body mass index
CFR	Code of Federal Regulations
CRF/eCRF	case report form/electronic case report form
ECG	electrocardiogram
ED	emergency department
EOT	end of treatment
EOS	end of study
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCRUQ	Healthcare Resource Utilization Questionnaire
HEOR	Health Economics Outcomes Research
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board

MedDRA	Medical Dictionary for Regulatory Activities
M.I.N.I.	Mini-International Neuropsychiatric Interview
MSQ	Medication Satisfaction Questionnaire
OC-VAS	Opioid Craving Visual Analog Scale
OD	overdose
OUD	opioid use disorder
PGx	pharmacogenomic(s)
PI	Principal Investigator
PK	pharmacokinetic(s)
PV	pharmacovigilance
RASS	Richmond Agitation-Sedation Scale
SAE	serious adverse event
SUD	Sedative, Hypnotic or Anxiolytic Use Disorder
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
TEA	Treatment Effectiveness Assessment
ULN	upper limit of normal
UDS	urine drug screen
US	United States
USPI	US Prescribing Information
VCU	Virginia Commonwealth University
WBC	white blood cell (count)
WHO	World Health Organization
WHODD	WHO Drug Dictionary
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

1 INTRODUCTION AND RATIONALE

1.1 Background and Rationale

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

1.1.1 Investigational Medicinal Product

SUBLOCADE™ (buprenorphine extended-release) injection is a colorless to amber sterile solution for SC injection designed to deliver buprenorphine at doses of 100 mg or 300 mg at a controlled rate over a one-month period. The active ingredient in SUBLOCADE injection 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 (NMP). Refer to the SUBLOCADE Investigator's Brochure (IB) or US prescribing information (USPI) 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 product. Occupational hazards and recommended handling procedures are provided in the USPI.

SUBOXONE sublingual film is supplied as an orange rectangular film with a white printed logo. Each SUBOXONE sublingual film contains buprenorphine HCl and naloxone HCl dihydrate at a 4:1 ratio expressed as the free bases. Films are intended for sublingual or buccal administration and are available in 4 dosage strengths (2 mg/0.5 mg; 4 mg/1 mg; 8 mg/2 mg; and 12 mg/3 mg). Refer to the SUBOXONE Sublingual Film USPI for additional information on the physical and chemical properties of the drug substance and for a list of excipients.

1.1.2 Dose Rationale

SUBLOCADE: SUBLOCADE is intended to be administered in this study as 300 mg monthly doses. If subjects are unable to tolerate the 300 mg dose as determined by the study investigator, the dose may be reduced to 100 mg monthly. The SUBLOCADE doses selected for this study have been shown to be efficacious in study RB-US-13-0001 (Double-Blind Efficacy). The doses tested in study RB-US-13-0001 were chosen to achieve and maintain patients at plasma exposures (≥ 2 ng/mL) that would achieve ≥ 70% brain mu-opioid receptor occupancy. This target plasma level and mu-opioid receptor occupancy was chosen based on data published by Greenwald (Greenwald 2003; Greenwald 2007) which showed that these levels were required to adequately control opioid withdrawal symptoms, opioid craving and to block the drug liking effects of an agonist when injected. Study RB-US-13-0002 (Opioid Blockade) showed that two 300 mg doses of SUBLOCADE injection dosed a month apart blocked the drug liking effects of an agonist when injected after treatment initiation with SUBLOCADE injection. However, wide variation can be seen in isolated measurements from individual subjects. Further details can be found in the IB and USPI.

The hypothesis is that SUBLOCADE will reduce the risk of a repeat opioid OD. This hypothesis is based on data showing that buprenorphine plasma exposures above 2 ng/ml will reduce the risk of an opioid OD in patients with OUD. Exposure-response relationships were assessed for illicit opioid use, and withdrawal symptoms using data obtained from 489 opioid dependent patients in the double-blind Phase 3 Study (RB-US-13-0001). PK data from the RB-US-13-0001 study show average buprenorphine plasma concentrations were below 2 ng/mL by 2 weeks after the first 300 mg injection. Average concentrations increased to greater than 2 ng/mL after the second 300 mg injection and remained above through to the 3rd injection, 28 days later.

To increase potential benefit in this population, the second 300 mg SUBLOCADE injection will be administered on day 8 (-0/+4 days) with subsequent injections being administered at 28-day (-2 / +4days of scheduled dosing days) intervals over approximately 6 months. Safety data from the SUBLOCADE Phase 3 program indicates this will not be a safety concern (average buprenorphine concentrations after the second 300 mg injection were lower than those observed at steady state).

SUBOXONE Sublingual Film: A single test dose of 4 mg/1mg SUBOXONE sublingual film will be administered to subjects in the ED prior to administration of the SUBLOCADE injection to ensure no allergic reaction or hypersensitivity to buprenorphine is present. This dose was selected as the targeted population have received an opioid antagonist for the treatment of an OD and are expected to be experiencing significant withdrawal symptoms.

1.1.3 Clinical Adverse Event Profile

The safety profile of SUBLOCADE injection observed in the Phase 3 studies (RB-US-13-0001, RB-US-13-0003 and INDV-6000-301) was generally consistent with the known safety profile of buprenorphine administered by the sublingual (SL) or buccal routes for the treatment of OUD with the expected exception of injection site tolerability and reactions.

The most common ADRs (reported by ≥5% of subjects) with SUBLOCADE were constipation, nausea, hepatic enzyme increased, headache, injection site pain, injection site pruritus, vomiting and fatigue. Injection site reactions were generally mild to moderate in severity, and none were serious. There were no unexpected safety findings. There was no increased risk of suicidality, and opioid OD was reported in <1% of subjects. There were no cases of SUBLOCADE injection OD reported. There was 1 death reported in the clinical development program, an SAE of gunshot wound with an outcome of death considered not related to study treatment and homicide by the police. There were no reports of subjects who attempted to remove the depot and no reports of buprenorphine OD or respiratory depression. No clinically significant trends in vital signs, electrocardiograms (ECGs), clinical laboratory tests or physical examinations have been noted in any of these studies.

The safety profile of SUBOXONE sublingual film is well characterized and, with the exception of the injection site reactions described above, is similar to that of SUBLOCADE.

1.2 Benefit-Risk Summary

Patients with OUD who survive an OD are at high risk of a subsequent OD. Treatment of OUD patients at high risk of OD (such as when released from incarceration), with methadone or buprenorphine reduces the risk of OD index cases by up to 85% (Marsden 2017). This supports treatment initiation as soon as possible after OD. The literature also supports a clear benefit of higher-dose MAT medications in patients at risk for opioid OD (Dupouy 2017, Marsden 2017, Sordo 2017). As noted above, SUBLOCADE at 300 mg administered subcutaneously on a monthly dosing regimen produces exposures at or above 2 ng/ml consistently, reaching higher exposures that appeared to be associated with improved outcomes. A potential advantage of using SUBLOCADE compared to transmucosal buprenorphine products in the emergency department (ED) following treatment for an opioid OD is the rapid achievement of plasma concentrations of 2 ng/ml buprenorphine which are sustained over the dosing interval. The risks associated with SUBLOCADE administered to patients with OUD in the ED are minimal, largely related to injection site reactions, precipitated withdrawal, or sedation which are significantly less than risk of repeat OD in this patient population.

Because there is a risk of sedation in patients who are not tolerant to opioid effects, patients who have a COWS of <8 and who were released from a controlled environment within the past 30 days will be observed for 2 hours after SUBLOCADE 300 mg administration and discharged with a RASS score > 0. This modification is intended to allow for enrolment of populations (i.e. patients who were recently incarcerated) that are especially vulnerable to opioid overdose due to a loss of opioid tolerance. Studies have shown that opioid overdoses are the leading cause of death in former prisoners in the immediate post-release period (Binswanger et al 2013).

2 STUDY OBJECTIVES

2.1 Primary

The primary objective of this study is:

- Determine the effect of SUBLOCADE treatment after opioid OD when administered in the ED setting, inpatient unit or within 7 days (168 h) of overdose in clinic on repeat OD and death compared to a historical control group and concurrent controls who decline treatment participation.

2.2 Secondary

The key secondary objective of this study is:

- Determine effect of SUBLOCADE when administered in the ED setting, inpatient unit or within 7 days (168 h) of overdose in clinic on treatment engagement at 3 months and 6 months comparing patients who have primarily intravenous to non-intravenous opioid use.

2.3 Exploratory

The exploratory objectives of this study are:

- To determine the effect of SUBLOCADE administered in the ED, inpatient unit or in the clinic within 7 days (168 h) of an opioid OD followed by SUBLOCADE administration monthly on the amount of opioid craving.
- To determine the efficacy of SUBLOCADE administered in the ED, inpatient unit or in the clinic within 7 days (168 h) of an opioid OD followed by SUBLOCADE in the clinic on opioid use as determined by Urine Drug Screen (UDS).
- To evaluate the effect of SUBLOCADE administered in the ED, inpatient unit or in the clinic within 7 days (168 h) of an opioid OD followed by SUBLOCADE in the clinic in the clinic on decision making using a delay discounting task and a brief opioid demand measure to measure craving valuation (hypothetical maximum price participants would be willing to pay for access to opioid, assessing craving/valuation).
- To evaluate the association between participant genetic polymorphisms and subjects with history of OD in subjects that consent to the PGx sub-study.
- To evaluate the relationship between genetics/behavioural laboratory measures of decision making and treatment outcome, including repeat OD in subjects that consent to the PGx sub-study.
- To determine the relationship between decision making and treatment retention and illicit opioid use.
- To evaluate healthcare resource utilisation associated with either treatment regimen as compared to the controls (2015-to end of data collection period) obtained from VCU anonymized health records.
- To assess the impact SUBLOCADE administered in the ED, inpatient unit or in the clinic within 7 days (168 h) of an opioid OD followed by administration of SUBLOCADE in

the clinic on treatment effectiveness as measured by Treatment Effectiveness Assessment (TEA), on medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ), and on employment, presentism and absenteeism as assessed by the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP).

3 STUDY ENDPOINTS

3.1 Primary

The primary endpoint of this study is:

- Time to repeat OD or opioid-related death. Repeat OD or opioid-related death will be measured from electronic medical records and state death registries.

- Additional comparisons on repeat OD and death rates will be made to concurrent patients who decline to participate in the SUBLOCADE injection.

3.2 Secondary

The key secondary endpoints of the study are:

- Numbers and percent of patients in buprenorphine treatment at 3 and 6 months after opioid OD comparing patients who have primarily intravenous to non-intravenous opioid use.

3.3 Exploratory

The exploratory endpoints of this study are:

- Opioid craving in subjects as measured by Craving Visual Analog Scale (VAS) scores.
- Illicit opioid use as measured by urine drug screen (UDS) results.
- Genetic predictors of treatment response and OD.
- Predictability of treatment response based on impulse control as measured by decision making in the delay discounting task, and opioid cravings/valuation as measured by the brief opioid demand task.

- Numbers of ED and hospital visits compared to the historical control (2015-2018) obtained from VCU anonymized health records.
- Scores on Treatment Effectiveness Assessment (TEA), medication satisfaction as measured by the Medication Satisfaction Questionnaire (MSQ), and employment, presentism and absenteeism as assessed by the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP).

3.4 Safety Assessments

Safety assessments include the proportion of subjects with AEs of the following types at any time during the treatment period: at least one AE, a drug-related AE, an SAE, a serious and drug-related AE, or an AE leading to treatment discontinuation**.**

Additional safety assessments include laboratory assessments, brief physical examinations, vital signs and concomitant medications.

3.5 Health Economics and Outcomes Assessments

Health economics and outcomes assessments include the Healthcare Resource Utilization questionnaire (HCRUQ, the Treatment Effectiveness Assessment (TEA), the Medication Satisfaction Questionnaire (MSQ), and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP).

3.6 Hypothesis and Treatment Comparisons

Participants who receive SUBLOCADE treatment regimen will have lower repeat OD and death rates compared to controls from electronic health record data. Prospective rates of OD will be based on ED data, self-report data, and Virginia death registry data.

4 STUDY PLAN

4.1 Study Design

4.2 Duration of Treatment

The total duration of study participation will be approximately 7 months. Subjects will be treated for 6 months with an End of Treatment (EOT) visit at 7 months.

Safety follow-up telephone calls will occur 30 days after the EOT Visit if the subject is continuing in treatment, with an additional 5 monthly phone calls (6 months total) if the subject is not continuing in MAT.

5 STUDY POPULATION SELECTION

5.1 Number of Subjects

Approximately 100 subjects will be enrolled.

5.2 Inclusion Criteria

Subjects must meet **all** of the following criteria:

1. Signed the informed consent form (ICF) and have the ability to comply with the requirements and restrictions listed therein.

2. Age: ≥ 18 years at time of executing the ICF.

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

4. Is clinically stable (respiratory rate [RR] ≥ 12, pulse oximetry > 95%, Glasgow Coma Scale [GCS] score of 15) and suitable for the trial in investigator's or designee's judgement.

5. Agrees not to take any buprenorphine products other than those administered during the current study throughout participation in the study.

6. Negative urine pregnancy test for females.

7. Vital signs (BP, HR, temperature) considered within normal limits or non-clinically significant elevation, as assessed by treating physician.

5.3 Exclusion Criteria

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

1. Current diagnosis, other than OUD, requiring chronic opioid treatment.

2. Active suicidal ideation in opinion of the Investigator or designee.

3. Female subject that is lactating, pregnant or planning to become pregnant during their participation in the study.

4. Uncontrolled intercurrent illness including, but not limited to, psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to provide written informed consent, signs of opioid toxicity more than 2 hours from naloxone administration or subjects with evidence of pulmonary edema.

5. Known allergy or hypersensitivity to SUBOXONE.

6. Any condition that, in the opinion of the Investigator would interfere with interpretation of subject safety or study results.

7. Currently receiving MAT for OUD (e.g. methadone, buprenorphine) or received methadone as a treatment for OUD within 30 days prior to consent.

8. Concurrent treatment with another investigational agent.

9. Concurrent enrolment in another clinical study, or observational study that includes MAT.

10. Treatment for OUD required by court order.

11. Current or pending incarceration/ legal action that could affect participation or compliance in the study.

12. Subjects who are unable, in the opinion of the Investigator, to comply fully with the study requirements.

13. Less than 48-72 hours since last use of long acting opioids (e.g., methadone), by self-report.

14. Current intoxication with benzodiazepines or alcohol.

15. Meet current DSM-5 diagnosis for severe Benzodiazepine or Alcohol Use Disorder, or endorse benzodiazepine or alcohol withdrawal symptoms.

16. Current illicit opioid users who endorse regular use of long acting opioids (e.g. methadone).

17. Total bilirubin ≥ 1.5x the upper limit of normal (ULN), alanine aminotransferase (ALT) ≥3xULN, aspartate aminotransferase (AST) ≥ 3xULN, serum creatinine > 2xULN, international normalized ratio (INR) >1.5xULN

18. Patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class lA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class Ill antiarrhythmic medications (e.g., sotalol, amiodarone) or other medications that prolong the QT interval.

5.4 Initial SUBLOCADE Dosing Criteria

In order to initiate SUBLOCADE dosing the following criteria must be met:

1) Clinically stable (respiratory rate [RR] ≥12, pulse oximetry > 95%, Glasgow Coma Scale [GCS] score of 15

2) No allergic reaction or hypersensitivity to SUBOXONE sublingual film.

3) More than 8 hours after the last dose of short acting opioid other than the SUBOXONE dose administered in the ED or at the clinic, or more than 48-72 after last dose of methadone.

6 STUDY CONDUCT

6.1 Subject Enrolment

Study participation begins once written informed consent is obtained; a subject ID is then assigned. The subject ID will be used to identify the subject during the screening process and throughout study participation, if applicable.

The Investigator is responsible for maintaining a master list (i.e., a subject identification list) of all consented subjects and will document all subjects that did not meet study eligibility criteria (i.e., screen failures), including reason(s) for ineligibility (i.e., a subject screening and enrolment log). Ineligible subjects, as defined by the protocol-specific inclusion and exclusion criteria, should not receive SUBLOCADE and should be documented as screen failures.

Controls will be selected from OD ED VCU visits beginning in 2015. The dataset will be anonymized; therefore, consent is not required and will not be obtained.

6.2 Screen Failure

A subject will be considered a screen failure if written informed consent is obtained but he/she does not meet inclusion / exclusion criteria or does not receive SUBLOCADE for another reason (example: the subject leaves prior to administration).

Subjects that screen fail may be re-screened for participation in the trial if they return to the ED, inpatient unit or outpatient treatment facility after a subsequent OD.

6.3 Subject Completion

6.3.1 Treatment Completion

Subjects that complete the EOT visit will be considered treatment completers.

6.4 Withdrawal and Stopping Criteria

6.4.1 Subject Withdrawal from Treatment

A subject will be considered withdrawn from treatment if the subject has permanently discontinued study treatment. The primary reason for withdrawal from treatment must be entered into the electronic case report form (eCRF) (e.g., death, AE, protocol non-compliance, investigator's decision, or as requested by the subject for another or unknown reason). Subjects who discontinue study treatment for any reason other than lost to follow-up will continue to be followed on an approximately monthly basis by telephone for repeat OD and treatment status and any scheduled HEOR assessments through to the end of their scheduled 30-day safety follow up telephone call.

Subjects who are withdrawn from the study for any reason after treatment with SUBLOCADE will not be replaced.

6.4.2 Subject Withdrawal from the Study

If the subject has permanently discontinued study treatment and monthly follow-up calls, 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., subject is lost to follow-up, or investigator's discretion).

Female subjects with confirmed pregnancies will be withdrawn from the study. See Protocol Section 12.2 for additional information.

6.4.3 Subject Withdrawal of Consent

If a subject withdraws consent, the primary reason should be entered into the eCRF. The subject will not receive any additional doses of study treatment. However, the subject may be offered additional tests as needed to monitor their safety (e.g., EOT safety assessments or procedures).

6.4.4 Subjects Lost to Follow-up

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

In the event a subject misses 5 consecutive weeks' worth of visits, they will be considered to have ceased treatment and withdrawn from the study. Investigators or designees must make a reasonable effort to contact the subject. Two documented attempts (e.g., phone, email, etc.) to contact the subject followed by a certified mailed letter is considered reasonable. Subjects who can no longer be contacted will be considered lost to follow-up.

For the purpose of documenting date of discontinuation for a subject confirmed to be lost to follow-up, the date of discontinuation will be the date of last in-person visit.

6.4.5 Liver Chemistry Stopping Criteria

Liver chemistry stopping criteria 1-5 are defined below:

1. The subject has ALT or AST >3 x ULN **and** bilirubin >2 x ULN (>35% direct bilirubin) (or ALT or AST >3 x ULN **and** international normalized ratio (INR) >1.5, if INR measured). Note: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT or AST >3 x ULN and bilirubin >2 x ULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, the presence of detectable urinary bilirubin on dipstick should be recorded, indicating direct bilirubin elevations and suggesting liver injury.

2. The subject has ALT or AST >8 x ULN.

3. The subject has ALT or AST >5 x ULN but <8 x ULN persisting for > 2 weeks.

4. The subject has ALT or AST >3 x ULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).

5. The subject has ALT or AST >5 x ULN but <8 x ULN and cannot be monitored weekly for >2 weeks.

6.4.5.1 Study Treatment Re-challenge

Study treatment re-challenge after liver chemistry stopping criteria are met by any study subject is not allowed. If clinically indicated, the SUBLOCADE depot may be surgically removed within 14 days of the injection.

7 STUDY SUSPENSION OR TERMINATION

In cases where a trial is suspended or terminated for safety reasons, the Principal Investigator (PI) will promptly inform the Regulatory Authorities of this action and the reason(s) for the suspension or termination.

If required by applicable regulations, the PI must inform the Institutional Review Board/Independent Ethics Committee (IRB/IEC) promptly and provide the reason(s) for the suspension or termination.

8 DESCRIPTION OF STUDY PROCEDURES

Study assessments and procedures, including the timing of assessments, are summarized in Appendix 1 and Appendix 2. Further details on efficacy assessments are provided in Section 8.6.

A signed written informed consent form must be obtained from the subject before any study assessments or procedures may be performed. At screening, if an assessment or procedure has already been performed as part of routine standard of care and was completed within the protocol-specific screening window, the assessment or procedure does not need to be repeated, unless clinically indicated. All assessments and procedures may be performed more frequently, if clinically indicated.

8.1 Demographics and Medical History

A detailed medical history will be obtained during the screening period. This will include information regarding the subject's complete history of relevant medical conditions, diagnoses, procedures, treatments, detailed history of drug use and any other noteworthy medical information. Any updates to medical history information made available during the course of the study will be captured.

8.1.1 DSM-5 Checklist for OUD, AUD and SUD and Mini-International Neuropsychiatric Interview (DSM 5 version)

At screening, the DSM-5 Checklist will be performed to assess for the presence and severity of OUD, AUD and SUD and will be reviewed by the PI or Sub-Investigator. At visit 2, the standardized diagnostic tool of the Mini-International Neuropsychiatric Interview (M.I.N.I), DSM-5 version (7.0.2) (Sheehan, 2016) will be used to screen for other DSM-5 substance-use disorders or other psychiatric co-morbidities.

8.2 Physical Examination

A brief physical examination will include an assessment of general appearance, lungs and cardiovascular system. The brief physical examination will occur in the ED, inpatient unit or at the clinic within 7 days (168 h) of the opioid OD at screening, and at the first clinic visit.

If any clinically significant change from screening is noted, it will be reported as an AE and followed up to resolution or until reaching a stable endpoint.

The Richmond Agitation-Sedation Scale (RASS) will be utilized to assess sedative effects of SUBLOCADE 300 mg in patients with COWS <8 and who were released from a controlled environment in the past 30 days (Sessler et al 2002). Patients with a RASS score > 0 will be eligible for discharge after a 2 hour wait period.

8.3 Vital Signs

Evaluation of vital signs will occur after the subject has been in a sitting position for ≥3 minutes and comprises systolic and diastolic blood pressure, pulse rate, respiratory rate, oxygen

saturation measurement and oral temperature. Any clinically significant vital sign measurements (as determine by the Investigator or a medically qualified designee) 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.

Vital signs will be recorded in the source document and the eCRF per the Schedule of Events (Appendix 1 and Appendix 2).

8.4 Treatment of Precipitated Withdrawal

Subjects experiencing precipitated withdrawal, may be treated symptomatically (SAMHSA TIP 63 2018):

- nausea: ondansetron or metoclopramide
- diarrhea: loperamide
- insomnia: diphenhydramine
- pain: nonsteroidal anti-inflammatory drugs

8.5 Clinical Laboratory Tests

Clinical laboratory tests will be performed at the time points listed in the Schedule of Events (Appendix 1 and Appendix 2) in a licensed clinical laboratory. Urine pregnancy tests and urine drug screens may be performed using a licensed point of care test (dipstick). Abnormal liver function tests (LFTs) will be followed at clinic visits according to investigator's judgement. An etiological evaluation will be performed if a hepatic adverse event (AE) is suspected.

Subjects are to be in a seated or supine position during blood collection.

The following clinical laboratory tests specified in Table 1will be performed.

Table 1 List of Laboratory Tests

Hematology:
Hematocrit
Hemoglobin
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean corpuscular volume
Platelet count
Red blood cell count
White blood cell count with 3-part differential

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

Additional Tests:
HIV
HCV B/C

Urine Drug Screen (UDS):

Opioids
Fentanyl
Buprenorphine
Methadone
Oxycodone
Amphetamines
Cannabinoids
Barbiturates
Benzodiazepines
Cocaine
Methamphetamines
Phencyclidine

Breath alcohol test

Serum Chemistry:
Albumin
Alkaline phosphatase
Alanine aminotransferase (ALT)
Amylase
Aspartate aminotransferase (AST)
Blood urea nitrogen
Calcium
Calculated creatinine clearance
Carbon dioxide
Chloride
Creatinine
Creatine kinase and subtypes
Gamma-glutamyl transferase
Globulin
Glucose (non-fasting)
Lactate dehydrogenase
Magnesium
Phosphorus
Potassium
Sodium
Total bilirubin
Direct bilirubin
Total cholesterol
Total protein

HIV = human immunodeficiency virus antibodies; HCB = Hepatitis B Virus; HCV = Hepatitis C virus.

8.5.1 Sample Collection, Storage, and Shipping

Samples will be analysed locally by an approved laboratory.

8.6 Efficacy Assessments

The primary measures of efficacy will be repeat OD and death data. Secondary measures will include treatment entry and retention. Additionally, results from Urine Drug Screening (UDS) and the Opioid Craving Visual Analogue Scale (OC-VAS) will be reviewed as exploratory measures.

8.6.1 Urine Drug Screen

Urine drug screening will be collected at every visit starting at Week 1 Day 2 as outlined in the Schedule of Events (Appendix 2).

8.6.2 Opioid Craving Visual Analog Scale (OC-VAS)

The OC-VAS is an instrument that measures a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. The amount of opioid craving that a subject feels for illicit opioids (not the buprenorphine used for treatment of OUD) can be recorded along a continuum from "no craving at all" to "strongest craving ever" (McMillan, 1996). Operationally, the OC-VAS is a horizontal line, 100 millimetres (mm) in length, anchored by word descriptors at each end. The subject indicates the point on the line that he/she feels represents his/her perception of their current state. The OC-VAS score is the difference from the left hand end of the line to the point that the subject marks. The OC-VAS will be performed before the SUBOXONE sublingual film test dose, before and after the SUBLOCADE injection and at each subsequent scheduled clinic visit as outlined in the Schedule of Events (Appendix 1 and Appendix 2).

8.7 Supportive Assessments

8.7.1 Delay Discounting Task

The delay discounting task is a hypothetical assessment of delay discounting (Koffarnus 2014) in which subjects choose between receiving a small amount of money immediately (e.g, $50 now) and a larger amount of money after a delay (e.g., $100 in 1 month). This task will be administered electronically as outlined in the Schedule of Events (Appendix 1 and Appendix 2).

8.7.2 Opioid Demand Task

Participants will complete a brief, hypothetical assessment of opioid craving/valuation in which they report the maximum amount of money they would pay to receive a dose of their preferred opioid drug. This task will be administered electronically as outlined in the Schedule of Events (Appendix 1 and Appendix 2).

8.7.3 Clinical Opiate Withdrawal Scale (COWS)

The COWS is an 11-item, validated instrument used to assess signs and symptoms of opiate withdrawal (Wesson 2003, Tompkins 2009). The score is the sum of the response to each of the 11 items 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. The COWS will be assessed by a qualified and trained individual throughout the course of the study. The COWS will be administered electronically and will be performed before the SUBOXONE sublingual film test dose, before and after the SUBLOCADE injection and at each subsequent scheduled clinic visit, as outlined in the Schedule of Events (Appendix 1).

8.8 Pharmacogenomic Assessment

Buccal swab samples for PGx analyses will be obtained following informed consent from the subject to participate in the optional PGx sub-study. No analyses, including genotyping and DNA sequencing, will be performed for personal identification. All samples will be identified by subject number and will not include any subject personal identifiers. The PGx samples are for genotyping. In the future, protein, RNA, metabolite studies or other research may be performed. Pharmacogenomic sample collection, handling, and storage are explained in greater detail in the laboratory manual.

8.9 Health Economics and Outcomes Assessments

Health economics and outcomes assessments will be collected at the time points listed in Appendix 1 and Appendix 2.

8.9.1 Treatment Effectiveness Assessment (TEA)

The Treatment Effectiveness Assessment (TEA) (Ling 2013) elicits subject responses that help the subject and the clinician to quickly gauge subject progress in treatment and in recovery. This progress is determined according to the subject's sense of what is important within four domains established by prior research. Improvement in each of the four recovery-oriented domains (substance use, health, lifestyle, and community) can be assigned a value of 1 (not improved or little improved) to 10 (very much improved) by the subject. The total score of improvement since treatment start is the sum of the responses to the four TEA domains, ranging from 4 (no measurable improvement or worse) to 40 (significantly improved). Subjects provide both numerical responses and representative details on their substance use, health, lifestyle, and community. In other words, the TEA assesses treatment progress and recovery, based on the subject's perspective.

8.9.2 Healthcare Resource Utilization Questionnaire (HCRUQ)

The HCRUQ will be completed by the Investigator or qualified designee and will collect hospitalizations; residential substance abuse treatment; general practitioner, specialist, and counselling visits; and Emergency Department (ED) visits. Also, The HCRUQ information will be obtained from informatics and electronic medical records from the respective site. It will

include information on medical services provided in the inpatient, outpatient, emergency department and other ancillary services available within the site's network.

8.9.3 Medication Satisfaction Questionnaire

The MSQ is a single-item questionnaire that evaluates satisfaction with medication (Vernon 2010). It is a subject-completed instrument with the following response levels. Responses are ordinal but can also be categorized into satisfied (5-7), neutral (4), or dissatisfied (1-3). The MSQ has shown an acceptable reliability (ICC>0.80) and validity (known groups, convergent and divergent validity) based on a randomized controlled trial with 191 schizophrenia patients (Vernon 2010).

8.9.4 Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI: SHP)

The impact of the disease and its treatment on work productivity and regular daily activities will be assessed by the WPAI Questionnaire (Reilly 1993). The WPAI questionnaire has 2 versions: WPAI-general health (WPAI-GH) and WPAI-Specific Health Problem (WPAI- SHP). In this study, WPAI-SHP will be used to target the measure to OUD. The WPAI-SHP has 6 items designed to measure employment, number of hours missed from work, and activity impairment during the past seven days due to the health problem. WPAI: SHP has been used among patients with OUD (Hoffman 2017).

8.10 Appropriateness of Measurements

The instruments used (e.g. COWS, OC-VAS, delay discounting task, opioid demand) were developed to measure the specific symptoms and or characteristics exhibited by individuals with opioid-dependence.

8.11 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or ICH/GCP requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. It is the responsibility of the Investigator and study site staff to use continuous vigilance to identify and report deviations to 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

9.1 Description

The term 'study treatment' is used throughout the protocol to describe any combination of product received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

9.1.1 Study Treatments

9.1.2 SUBLOCADE

SUBLOCADE injection is a colorless to amber sterile solution for SC injection designed to deliver buprenorphine at doses of 100 mg or 300 mg at a controlled rate over a one-month period. The active ingredient in SUBLOCADE injection is buprenorphine free base, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist. Buprenorphine is dissolved in ATRIGEL at 18% by weight and is a biodegradable 50:50 poly (DL-lactide-co-glycolide) polymer and a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). Refer to the IB or prescribing information 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 product. Occupational hazards and recommended handling procedures are provided in the prescribing information.

9.1.3 SUBOXONE Sublingual Film

SUBOXONE sublingual film is an orange rectangular film with a white printed logo. Each SUBOXONE sublingual film contains buprenorphine HCl and naloxone HCl dihydrate at a 4:1 ratio expressed as the free bases. Films are intended for sublingual or buccal administration and are available in 4 dosage strengths (2 mg/0.5 mg; 4 mg/1 mg; 8 mg/2 mg; and 12 mg/3 mg). Refer to the SUBOXONE Sublingual Film USPI for additional information on the physical and chemical properties of the drug substance and for a list of excipients.

SUBOXONE sublingual film is commercially available and will be obtained by VCU Health System Pharmacy.

9.1.4 Blinding

This is an open-label trial with no blinding.

9.2 Packaging and Storage

SUBLOCADE study labels will be developed in accordance with GMP and local regulatory requirements. SUBLOCADE will be individually numbered.
SUBLOCADE injection is supplied as a prefilled syringe. SUBLOCADE will be packaged and labelled in a manner consistent with the study design and applicable regulations. The packaging includes an outer carton with an inner pouch which contains the pre-filled syringe, oxygen absorber and a sterile 19-gauge, 5/8-inch hypodermic safety needle.

SUBLOCADE should be stored in a secure location in accordance with federal, state and local requirements for storage of Schedule III Controlled Substance under refrigerated conditions between 2ºC to 8ºC (36°F to 46°F). Once outside the refrigerator, SUBLOCADE may be stored in its original packaging at room temperature (15°C to 30°C, [59°F to 86°F]), for up to 7 days prior to administration. Discard SUBLOCADE if left at room temperature for longer than 7 days.

Study treatment must be handled strictly in accordance with the protocol and applicable local laws and regulations.

SUBOXONE sublingual film is an orange rectangular sublingual film with a white printed logo. SUBOXONE is supplied in boxes of 30 count film strips. SUBOXONE sublingual films should be stored at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F).

9.3 Drug Administration

9.3.1 SUBLOCADE Injection

SUBLOCADE injection will be administered following confirmation that the subject meets all eligibility and continuation criteria. The designated study treatment should be administered under the supervision of the Investigator, a suitably qualified member of the study team, or by a pharmacist. The Investigator or designee agrees not to administer SUBLOCADE from, or store it, at any location other than the study site agreed upon with the Indivior. Detailed instructions related to preparation of SUBLOCADE injection are outlined in the Prescribing Information.

SUBLOCADE subcutaneous (SC) injection sites should be rotated (see USPI for details) and the product must not be administered intravenously or intramuscularly. Eligible subjects will receive up to 7 subcutaneous injections of SUBLOCADE injection as outlined in the SOE (Appendix 1 and Appendix 2). No injections are permitted outside of the protocol-specified window without the approval of the PI. Detailed instructions regarding the administration of SUBLOCADE injections are located in the USPI.

Time of dose is defined as the time the SUBLOCADE 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 SUBLOCADE injection to any person except study personnel for SC injection of subjects in this study.

Adequate precautions must be taken to avoid direct contact with SUBLOCADE injection. Occupational hazards and recommended handling procedures are provided in the SUBLOCADE USPI.

9.3.2 SUBOXONE Sublingual Film

On Day 1, SUBOXONE sublingual film (4 mg/1 mg) will be administered in the ED, inpatient unit or at the clinic within 7 days of the opioid overdose event.

SUBOXONE sublingual film can be administered by the sublingual or buccal routes. Sublingual Administration: Place one film under the tongue, close to the base on the left or right side and allow to completely dissolve. Buccal Administration: place one film on the inside of the left or right cheek and allow to completely dissolve. For more information on SUBOXONE sublingual film administration, refer to the prescribing information.

9.4 Accountability

The Investigator is responsible for ensuring that SUBLOCADE received at the site is inventoried, accounted for and documented in accurate study treatment accountability records and filed in the eCRF. A record of the number of SUBLOCADE injections and associated lot and kit number administered to each subject must be maintained and reconciled with the eCRF. Unused SUBLOCADE injection will be destroyed on-site and documented per VCU health guidelines.

A record of the SUBOXONE sublingual film test dosage and time of administration will be recorded in the source.

9.5 Reporting Product Complaints

The Investigator and study site staff are responsible for prompt recognition and reporting of product quality complaints to Indivior. A product complaint is any concern pertaining to the manufacturing or quality control of the product and includes, but is not limited to, the quality and quantity of a drug product, labelling defects, missing inserts, packaging defects or difficult to open packaging, product that is thought to be ineffective, or has an appearance, taste or odour that is outside of what is expected.

All product complaints should be reported to Indivior within one (1) business day after identifying the **issue** using the following email address: **R&DQA@indivior.com** and provide the following information:

- PI Name
- Site contact/reported by
- Product description including unit or kit number for individually numbered units.
- Subject Number (if already assigned to a subject)
- 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.

9.6 Concomitant Therapies

Concomitant medications will be collected from screening until the EOS visit at the time points listed in the SOE (Appendix 1 and Appendix 2). 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.

9.6.1 Permitted Concomitant Therapies

The Investigator may prescribe concomitant medications or treatments deemed necessary to the subject, with the exception of those medications defined in Section 9.6.3 of the protocol.

9.6.2 Drug-Drug Interactions

Due to additive pharmacologic effects, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.

The SUBLOCADE prescribing information should be referenced regarding use of the below concomitant therapies.

- Benzodiazepines and Other Central Nervous System (CNS) Depressants
- Cytochrome P450 3A4 Inhibitors
- Cytochrome P450 3A4 Inducers
- Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Antiretrovirals: Protease Inhibitors (PIs)
- Serotonergic Drugs
- Monoamine Oxidase Inhibitors (MAOIs)
- Muscle Relaxants
- Diuretics
- Anticholinergic Drugs

9.6.3 Prohibited Concomitant Therapies

Subjects should be instructed not to take any medications, including over-the-counter products, without first discussing with the Investigator.

Concomitant use of buprenorphine or methadone is prohibited.

9.7 Compliance

SUBOXONE sublingual film will be administered in the ED, inpatient unit or at the clinic within 7 days (168 hours) of opioid OD and documented in the source and recorded in the eCRF.

SUBLOCADE will be administered by licensed healthcare provider, delegated by the Investigator, in the ED and out-patient as delegated by the Investigator. Injection sites will be assessed for evidence of attempted removal of the depot by the subject. The assessment and any findings will be documented in the source and recorded in the eCRF. Likewise, surgical removal by a physician will be documented in the source and recorded in the eCRF.

Use of prohibited concomitant medications will be evaluated per the Concomitant Medication assessment outlined in the Schedule of Events (Appendix 1 and Appendix 2), documented in the source and recorded in the eCRF.

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 subject associated with the use of an IMP regardless of the presence of a causal relationship to the IMP. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with an IMP, whether or not considered related to the IMP.

Events meeting the definition of an AE include:

- New condition detected after IMP administration even though the AE may have been present prior to receiving IMP.
- 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 or an OD of either IMP or a concomitant medication.
- Signs, symptoms or the clinical sequelae resulting from special interest conditions (e.g., medication error, IMP withdrawal, injection site tampering resulting in removal of the depot etc.). Overdose per se will not be reported as an AE/SAE unless this is an intentional OD 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 subject'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, hospitalization for elective surgery, hospitalization 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 Assessment of 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 IMP will be reported as described in this protocol.

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

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

10.1.1 Time Period for Collecting Adverse Events

Adverse events will be collected from the time of signed informed consent until completion of the EOT visit. SAEs will be reported through the end of the safety follow-up period.

Ongoing SAEs at the safety follow-up phone call that, in the opinion of the Investigator, are associated with the IMP, will be followed and reported as described in Section 11.2.

All SAEs that, in the opinion of the Investigator, are associated with the IMP will be followed to resolution.

In the event a subject misses 5 consecutive weeks' worth of visits, they will be considered to have ceased treatment and withdrawn from the study. Investigators or designees must make a reasonable effort to contact the subject. Two documented attempts (e.g., phone, email, etc.) to contact the subject followed by a certified mailed letter is considered reasonable. Subjects who can no longer be contacted will be considered lost to follow-up.

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

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

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

10.1.3 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 IMP.

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

Not Related:	Data are available to identify a clear alternative cause for the AE other than the IMP.
Related:	The cause of the AE is related to the IMP and cannot be reasonably explained by other factors (e.g., the subject'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 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 IMP will be considered and investigated. The Investigator will also consult the IB and/or USPI, for marketed products, 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 has occurred and the Investigator has minimal information to include in the initial report. However, it is imperative that the Investigator always make an assessment of causality for every event prior to the initial transmission of the SAE 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 data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.1.4 Clinical Laboratory Changes

Changes in laboratory values, vital signs or other safety parameters (e.g., neurological and clinical symptom assessments) as noted in the protocol are a subset of Aes and are reportable only if 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 IMP, or a change to dosing other than as permitted by protocol, or if considered to be clinically significant by the Investigator or medically qualified designee.

Screening laboratory assessments, if determined to be clinically significant by the Investigator, are not Aes.

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

11 SERIOUS ADVERSE EVENTS

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 hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received SUBLOCADE injection
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 hospitalization
- Potential Hy's Law cases indicative of medication-induced hepatocellular injury, defined as:
    - ALT or AST >3x ULN and total bilirubin of >2x ULN (or INR >1.5 if measured) with no other reason found to explain combination of increased ALT and total bilirubin, such as hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury. Note: INR threshold does not apply to subjects receiving anticoagulants
    - ALT or AST >3x ULN with systemic symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [> 5%])

Potential Hy's Law cases should be managed as described in Appendix 3.

An AE is considered "life threatening" if the subject 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, IMP-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though IMP-induced hepatitis can be fatal.

Adverse events requiring hospitalization should be considered SAEs. Hospitalization 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, hospitalization signifies that the subject 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 hospitalization are Aes. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' 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 subject's ability to carry out normal life functions.

11.1 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 form in the eCRF.

It is not acceptable for the Investigator to send photocopies of the subject'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 subject identifiers, with the exception of subject 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 Reporting Serious Adverse Events

11.2.1 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 the IRB by the Investigator (or designee) **within 24 hours** from first being aware of the event by completing the appropriate eCRF(s). Any follow-up information on a previously reported SAE will also be reported to the IRB within 24 hours.

Where additional information is needed or expected, the Investigator will not wait to receive all information before reporting the event to the IRB. The Investigator must provide an assessment of causality at the time of the initial report as described in Section 10.1.3 of the protocol.

Indivior will be informed of SAEs within 24 hours of from the Investigator first becoming aware of the event by using the form provided by Indivior. Any follow-up information on a previously

reporting SAE will be reported to Indivior within 24 hours of the Investigator becoming aware of the update.

Reporting email address: **PatientSafetyNA@Indivior.com**

11.2.2 Regulatory Reporting Requirements for Serious Adverse Events

Prompt receipt of notifications of SAEs to the IRB or designated representative from investigators is essential in ensuring that legal obligations and ethical responsibilities regarding the safety of subjects are met.

A suspected unexpected serious adverse reaction (SUSAR) is an SAE related to the IMP administered in any dose and that, in its nature or severity, is inconsistent with the IB or Product Information for marketed products.

11.2.3 Overdose

Any instance of intentional OD (whether or not it involved IMP) must be communicated as an SAE and fully documented. Details of any signs or symptoms and their management should be recorded, including details of any antidote(s) administered.

11.2.4 Depot removal

Any instance of depot removal (by a clinician, or injection site tampering by the study subject resulting in removal of the depot) will be considered as an AE of special interest and must be communicated to Indivior or designated pharmacovigilance (PV) representative (email address for reporting: PatientSafetyNA@Indivior.com) within 24 hours of the Investigator first becoming aware of the event by using the SAE reporting form provided by the Indivior (seriousness criteria to be left unticked, if applicable).

12 PREGNANCY

12.1 Collecting and Reporting Pregnancy Information

All pregnancies will be collected from receipt of IMP through the scheduled 30-day follow-up phone call. Subjects who do not continue in MAT will have pregnancies collected until 5 terminal half-lives following the last dose of IMP. For this IMP this period is approximately 12 months. 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 subject without associated unexpected or adverse sequelae is not a reportable AE, but must be reported to Indivior or designated PV representative (email address for reporting: PatientSafetyNA@Indivior.com), using the Clinical Trial Pregnancy Reporting Form within 24 hours of the Investigator first being aware of the pregnancy.

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; however, additional follow-up for up to 2 years may be required if there are any complications for the infant. 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 subject has completed the study and considered by the Investigator as possibly related to the study treatment, must be promptly reported to Indivior or designated PV representative. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

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

If a female subject suspects that she is pregnant (e.g., missed period, self-administered pregnancy test) during treatment or within 6 months after the discontinuation of SUBLOCADE, she should return to the clinic as soon as possible to undergo a urine pregnancy test. Subjects will receive a card with clinic information at the screening visit, including instructions on follow-up should they suspect pregnancy (follow up with the clinic or their usual place of care).

If pregnancy is confirmed at any time during the study, the subject will be withdrawn from study treatment and will undergo all final study visit procedures (with the exception of any additional pregnancy testing) and continue with monthly telephone follow-up. Subjects who are determined to be pregnant will be referred to the VCU outpatient obstetrics clinic or other obstetrics clinic in the local vicinity if they do not wish to attend the VCU clinic.

The Investigator should fully inform the female subject of the potential risk to the fetus as well as discuss the desirability of continuing the pregnancy.

13 DATA MANAGEMENT

13.1 Data Collection and Management

Data will be entered into the eCRF. 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 WHO Drug Dictionary (WHO-DD).

13.1.1 Historical and Concurrent Control Data

The historical and concurrent control data used for exploratory OD comparison analyses will be provided by Virginia Commonwealth University as an anonymized data extract from their electronic medical record system beginning in 2015. Data will include, but not be limited to; demographics, discharge diagnoses and status and ICD 9/10 codes.

13.1.2 Database Quality Assurance

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

13.1.3 Source Documents

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

Study data are to be gathered onto primary source documents at the clinical site, except for certain assessments to be captured as direct entry on a tablet as indicated in the next paragraph. Completion of source documents will precede the completion of the CRF. 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 authorized study personnel outlined in the ICF. The CRF will be considered the source document for individual CRF elements such as study-specific scales if those data are collected directly onto a CRF.

The following assessments will be collected as direct data entry:

- HCRUQ
- COWS
- OC-VAS

- Opioid Demand Task
- Delay Discounting Task
- HEOR assessments

14 STATISTICS

14.1 General Procedures

This section describes methods for sample size determination, analysis populations and planned analyses. Additional unplanned analyses may be required after all planned analyses have been completed. Any unplanned analyses will be clearly identified in the clinical study report.

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

14.2 Sample Size

The study will be powered based upon the primary endpoint, repeat opioid OD and death compared to historical and concurrent control data.

Rationale for sample size: Power calculations: sample size was calculated based on a primary outcome measure of reduced repeat opioid OD rates. Previous research has shown self-reported repeat lifetime OD rates of 15-23% for patients who were seen for an opioid OD (Morizio, Baum et al. 2017).

Based on VCU health system data, for patients seen in the ED for an opioid OD in 2016, 11.5% of those patients were either seen again in the ED for an opioid OD or had died based on Virginia Department of Health death registry data within 6 months after their initial ED visit. Based on power calculations below, with a 3% repeat OD or death rate for the novel treatment group vs. the 11.5% treatment as usual rate in the historical control group, with 99 participants in the novel treatment group and 198 participants in the historical control group there will be a power of 80% at a type I error rate of 5%. See table below. If there is a less than 3% repeat OD rate in the intervention group there will be greater than 80% power.

Fixed Power of 0.80 and sample size for equivalent or non-equivalent numbers of participants per group (intervention vs. historical treatment as usual)

repeated OD/death rate	Stat method	n1:n2 (1:1, 2:1 or :1 ratio)		
11.5% vs 2%	Z-test	86:86	117:59	148:49
	Nonparametric	94:94	148:74	198:66
11.5% vs 3%	Z-test	115:115	160:80	204:68
	Nonparametric	131:131	198:99	265:88

14.3 Statistical Hypotheses

14.3.1 Primary Endpoint

The primary hypothesis is that SUBLOCADE is superior to the historical and concurrent control group for rates of repeat OD and death during the 6 months treatment period.

14.4 Analysis Populations

14.4.1 Treatment Population

The Treatment Population includes all subjects who receive at least 1 dose of study medication. This population will be used for all safety and efficacy analyses. In the safety analyses, subjects will be analysed according to treatment actually received.

14.5 Planned Analyses

The analysis will take place once all subjects have completed the trial and sufficient time has passed to allow the state death registries to be updated.

14.6 Demographic and Baseline Characteristics Analyses

Demographic and baseline characteristics, including gender, race, age, weight, height and disease history will be summarized by treatment group using descriptive statistics. Disease history will include but is not limited to drug use history, history of MAT and previous Ods. Qualitative variables, e.g. gender and race will be summarized using frequencies; quantitative variables, e.g. age, weight, height will be summarized using e.g. mean, SD, median, minimum and maximum.

14.7 Efficacy Analysis

14.7.1 Primary Efficacy Analysis

The repeat opioid OD or opioid-related death primary endpoint analysis will be performed using Cox proportional regression and compare the SUBLOCADE treatment arm to historical and concurrent control data. Propensity scores will be used to match study participants to controls. Repeat OD and deaths (measured as time-to-event or censored at 6 months post index OD) will be tracked using subject reports, electronic medical records and state death registries. Events will be counted within the 6 months of treatment period for all treated subjects.

Propensity score analysis will be used in the analysis of SUBLOCADE vs. the control for time to repeat OD or opioid-related death. Study subjects will receive a propensity score that will be matched to propensity scores in the control data. The propensity score, p, will also be used as a weight in the Cox proportional hazards model. All SUBLOCADE treatment group subjects will have a weight of p=1 and patients in the control groups will be weighted by p/(1-p). Here p can be viewed as the probability that the control subject would have been a study participant if the study were performed during their treatment.

The propensity score will be estimated by fitting a logistic regression on a dataset consisting of the consenting subjects (subjects in the SUBLOCADE arm at VCU) and the controls. The response variable will be consent to treatment; predictors will include baseline characteristics such as subject age, gender, county, race and insurance status. This model will be used to generate the predicted probability of consent to participate among the controls.

The Cox proportional hazards model will use the controls as the reference group and code the SUBLOCADE arm as a factor variable. The analysis will test the coefficient for the SUBLOCADE arm versus the controls from the Cox regression, with the interpretation of the exponential (coefficient) as the hazard ratio for time to repeat OD or opioid-related death in subjects consenting to the active treatment group versus the control cohorts.

The probabilities for the control cohort will be used as weights in the Cox proportional hazards model. The weights serve to make the control cohort appear similar to the treatment group on the observed baseline characteristics; this will be checked using covariate balance diagnostics. The weights will provide greater weight for control patients who likely would have participated if offered a prospective trial of SUBLOCADE and lesser weight for patients unlikely to have consented.

In addition, the results will be illustrated with a Kaplan-Meier curve.

The analysis will take place once all subjects have completed the trial and sufficient time has passed to allow the state death registries to be updated.

14.7.2 Secondary/Exploratory Endpoint Analysis

Treatment retention at 3 and 6 months will be analysed utilizing a logistic regression, comparing subjects who have primarily intravenous to non-intravenous opioid use as determined using the MINI.

The analysis of the exploratory endpoints (incidence rate of repeat OD, illicit opioid use as measured by UDS and opioid craving, as measured by the OC-VAS) is detailed in Table 2.

These analyses will be performed using the treatment population.

A summary of the primary, secondary, and exploratory endpoint analyses is shown in Table 2.

Table 2 Summary of Efficacy Analysis Strategy

Endpoint	Statistical Method	Analysis Population	Missing Data Approach	Analysis Timepoint
Primary Efficacy Endpoint:				
Repeat OD or Death	Propensity scores within Cox PH Regression	Treatment	No imputation	EOT (6 months)
Secondary Efficacy Endpoints:				
Treatment retention at 3 and 6 months	Logistic Regression	Treatment	No imputation	EOT (6 months)
Exploratory Endpoints:				
Illicit opioid use as measured by urine drug screen (UDS) results	Hierarchical generalized linear modeling (HGLM)	Treatment	Missing UDS during treatment will be imputed as non-negative for opioids. Missing UDS if lost to follow-up will be imputed as missing.	EOT (6 months)
Opioid craving in subjects as measured by Craving Visual Analog Scale (VAS) scores.	Logistic Regression, ANCOVA	Treatment	No imputation	EOT (6 months)
Genetic predictors of treatment response and repeat OD.	Logistic Regression, ANCOVA	Treatment [a]	No imputation	EOT (6 months)
Predictability of treatment response based on impulse control as measured by decision making in the delay discounting task.	Logistic Regression, ANCOVA	Treatment	No imputation	EOT (6 months)
Retention in treatment between ED initiated Suboxone/Sublocade compared to Outpatient initiated Suboxone/Sublocade	Cox PH Regression	Treatment	No imputation	EOT (6 months)

a This analysis will only include subjects within the treatment population that consented to participate in the PGx sub-study.

14.7.2.1 Health Economics & Outcomes Analyses

Treatment Effectiveness Assessment (TEA)

HEOR endpoints relating to the TEA will be described as change from baseline score to each follow-up assessment and end of treatment (EOT). Absolute scores by study visit will also be reported and compared between treatment groups. The absolute score and/or change from baseline score at EOT will be considered the primary variable of interest in these analyses.

Baseline will be defined as the last assessment on or before Week 3 Day 15±4 (Visit 4). (See Appendix 2- Treatment Clinic Schedule of Events)

MEDICATION SATISFACTION QUESTIONNAIRE (MSQ)

The percentage of subjects reporting each response on the MSQ will be reported by study visit and EOT. The percentage of subjects reporting that they are satisfied (score 5-7) at the EOT will be considered the primary variable of interest in these analyses.

WORK PRODUCTIVITY ASSESSMENT INSTRUMENT: SPECIFIC HEALTH PROBLEM (WPAI:SHP)

For the WPAI:SHP, the percentage of patients employed, percentage absenteeism, percentage work impairment, and percentage activity impairment will be reported at baseline, each follow-up assessment and EOT by treatment arm. The change in percent employed from baseline to each follow-up assessment will be assessed. Among those employed at baseline and the respective follow-up assessments, the changes from baseline in percentage absenteeism, percentage work impairment and percentage activity impairment at each follow-up assessment will be assessed. The change in percent employed from baseline to EOT; and among those employed at baseline and EOT, the changes in percentage absenteeism, percentage work impairment and percentage activity impairment from baseline to EOT will be considered as primary variables of interest in these analyses.

Baseline will be defined as the last assessment on or before Week 3 Day 15±4 (Visit 4). (See Appendix 2- Treatment Clinic Schedule of Events)

HEALTHCARE RESOURCE UTILIZATION QUESTIONNAIRE(HCRUQ)

Frequency of use by HCRUQ type will be summed throughout the study period, from Week 1 to EOT (or last visit with available data for subjects who discontinue treatment prematurely), to arrive at a total use while in the study. The incidence of HCRUQ by type will be assessed, dividing by the total amount of follow-up time in each group. Types of hospitalisations, emergency room, and outpatient service visits will be categorized (e.g., medical, surgical, psychiatric). Hospital days will be calculated as the sum of all inpatient days during the study.

For continuous measures, 95% confidence intervals will be provided for comparisons of statistics between treatments. Unless otherwise specified, the absolute value of continuous outcome measures will be analysed using a mixed model for repeated measures (MMRM). A test of proportions (for example: exact test) will be used to evaluate treatment differences for categorical outcome variables.

14.7.3 Exploratory Analysis

Genetic predictors of treatment response and outcomes analysis will include a study of polymorphisms in candidate pharmacokinetic and pharmacodynamic genes in subjects that consent to the optional PGx sub-study with an aim of understanding the role of genetic variants in modifying the risk of future OD and to determine treatment outcomes. This analysis will include all subjects that consented to participate in the PGx sub-study.

The predictability of treatment response based on impulse control analysis will be performed using logistic regression models predicting treatment success (e.g., point prevalence opioid abstinence, treatment retention) as a function of baseline delay discounting, and opioid craving/valuation. Additionally, possible changes in delay discounting and craving/valuation over the course of treatment will be modelled using repeated measures analysis of covariance (ANCOVA), including time as a within-subjects factor, and relevant demographic and substance use measures as covariates. This analysis will be performed using the treatment population.

14.7.4 Subgroup Analysis

Primary analyses will be repeated but adding an explanatory class variable of subjects identified as injectors vs. non-injectors at Week 1 Day 1 (Visit 1).

14.8 Handling of Missing Data

In general, missing data (caused by premature discontinuation or otherwise) will not be imputed. However, missing urine drug screen data will be imputed based on previously defined methods in other patient populations. The secondary endpoint is time attending clinic and patients failing to appear will be considered to have stopped attending at the date of last visit after they've missed 5 consecutive visits. Any missing covariates will be handled via appropriate multiple imputation techniques.

14.9 Analysis of Safety

Safety variables will include AEs, concomitant medications, laboratory tests (haematology, chemistry and urinalysis), vital signs, and medical history. Safety variables will be analysed on the treatment population using descriptive statistics for continuous endpoints (e.g. mean, median, SD, minimum and maximum) and frequency counts with percentages for discrete endpoints.

Baseline is defined as the last available assessment prior to dosing on Week 1 Day 1 (Visit 1).

14.9.1 Adverse Events

All AEs will be coded using MedDRA, summarized by treatment arm and reported to FDA. Adverse events that begin prior to SUBLOCADE administration or after the 6 month visit will be presented separately. Only AEs occurring after SUBLOCADE administration will be included in the analysis.

14.9.2 Extent of Exposure

The duration of treatment with SUBLOCADE, defined as the date of the last injection minus the date of first injection +28 days, will be summarized as a continuous summary.

The total number of SUBLOCADE injections will be presented as a continuous summary and a categorical summary. The number of subjects who had early surgical removal of SUBLOCADE depot will be summarized.

14.9.3 Laboratory Data

Summary statistics for absolute laboratory value will be presented.

14.9.4 Vital Signs

Summary statistics for vital signs will be presented.

14.9.5 Other Safety-Related Variables

Medical history will be coded using MedDRA and summarized by treatment group. Body weight, height and BMI will be summarized using descriptive statistics (mean, median, SD, minimum and maximum), including change from baseline.

Prior and concomitant medications will be coded using WHO-DD. Incidence (number and percent of subjects reporting the medication at least once during the study) will be summarized for all concomitant medications.

15 ETHICS AND RESPONSIBILITIES

15.1 Good Clinical Practice

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

15.2 Institutional Review Board/Independent Ethics Committee

The protocol, ICF(s) and any other written information and/or materials to be provided to subjects will be reviewed by an independent and appropriately constituted IRB/Independent Ethics Committee (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.

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

15.3 Informed Consent

The Investigator or a person designated by the Investigator is to obtain written informed consent from each subject 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.

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 subject 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 subject that participation is voluntary, and that consent can be withdrawn at any time and without reason. Subjects 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 signed ICF should be updated accordingly. All subjects 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.

15.4 Records Management

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 Inc. 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 (subject records, subject 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 for 5 years after the end of the study.

16 MONITORING

In accordance with applicable regulations, GCP, clinical monitor(s) will periodically review all study data for accuracy and completeness as described in the Clinical Monitoring Plan.

The PI 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 in conjunction with the PI, as appropriate.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centres, review of protocol procedures with the investigators and associated personnel before the study. Written instructions will be provided for study drug preparation and dosing, collection, preparation, and shipment of blood, plasma and urine samples are available in the prescribing information.

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

This study is subject to inspections by Regulatory Authorities. If such a regulatory inspection occurs, the PI agrees to allow the regulatory inspector direct access to all relevant study documents. The PI must contact Indivior Inc. immediately if this occurs and must fully cooperate with the inspection conducted at a reasonable time in a reasonable manner.

17 AMENDMENTS

A protocol change intended to eliminate an apparent immediate hazard to subjects 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. The Investigator or designated representative will submit protocol amendments to the appropriate Regulatory Authorities for approval.

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

18 STUDY REPORTS AND PUBLICATIONS

A clinical study report will be prepared following completion of the study. Study results will be published on clinicaltrials.gov and in a peer reviewed journal.

19 STUDY TERMINATION

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

20 CONFIDENTIALITY

All subject-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 subject. However, authorized regulatory officials will be allowed full access to inspect and copy the records. All subject bodily fluids and/or other materials collected shall be used solely in accordance with this protocol and the ICF signed by the subject, unless otherwise agreed to in writing by Indivior Inc.

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

21 REFERENCES

Binswanger, Ingrid A., et al. "Mortality after prison release: opioid overdose and other causes of death, risk factors, and time trends from 1999 to 2009." *Annals of internal medicine*159.9 (2013): 592-600.

Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Med Care. 2004 Sep;42(9):851-9.

Cushman PA, Liebschutz JM, Anderson BJ, Moreau MR, Stein MD. Buprenorphine initiation and linkage to outpatient buprenorphine do not reduce frequency of injection opiate use following hospitalization. J Subst Abuse Treat. 2016 Sep;68:68-73.

Dupouy J, Palmaro A, Fatséas M, Auriacombe M, Micallef J, Oustric S, Lapeyre-Mestre M. Mortality associated with time in and out of buprenorphine treatment in French office-based general practice: a 7-year cohort study. Ann Fam Med. 2017;15:355-8.

Greenwald MK, Johanson C-E, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta J-K. Effects of buprenorphine maintenance dose on μ-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropharmacol. 2003;28:2000-9.

Greenwald MK, Johanson C-E, Bueller J, Chang Y, Moody DE, Kilbourn M, Koeppe R, Zubieta J-K. Buprenorphine duration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. Biol Psychiatry. 2007;61:101-10.

Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerstrom Test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict. 1991 Sep;86(9):1119-27.

Hoffman K, Peyton ML, Sumner M. Safety of a rapidly dissolving buprenorphine/naloxone sublingual tablet (BNX-RDT) for treatment of opioid dependence: a multicenter, open-label extension study. J Addict Med. 2017 May/Jun;11(3):217-23.

ICH: M3(R2) Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals [Internet]. International Council on Harmonisation 2009 [cited 2016 May 23]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009 Aug;37(8):1779-84.

Koffarnus MN, Bickel WK. A 5-trial adjusting delay discounting task: Accurate discount rates in less than one minute. Exp Clin Psychopharmacol. 2014 Jun;22(3), 222-8.

Liebschutz JM, Crooks D, Herman D, Anderson B, Tsui J, Meshesha LZ, Dossabhoy S, Stein M. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. JAMA Intern Med. 2014;174(8):1369-1376.

Ling W, FarabeeD. Liepa D, Wu, LT. The Treatment Effectiveness Assessment (TEA). Subst AbuseRehabil. 2013 Sep;4:73-4.

Marsden J, Stillwell G, Jones H, Cooper A, Eastwood B, Farrell M, Lowden T, Maddalena N, Metcalfe C, Shaw J, Hickman M. Does exposure to opioid substitution treatment in prison reduce the risk of death after release? A national prospective observational study in England. Addiction. 2017 Aug;112(8):1408–18.

McMillan DE, Gilmore-Thomas K. Stability of opioid cravings over time as measured by visual analog scales. Drug Alcohol Depend. 1996 Mar; 40(3):235-9.

Mercado MC, Sumner SA, Spelke MB, Bohm MK, Sugerman DE, Stanley C. Increase in drug overdose deaths involving fentanyl—Rhode Island, January 2012-March 2014. Pain Med. 2018 Mar;19(3):511-23.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993 Nov;4(5):353-65.

Sessler, Curtis N., et al. "The Richmond Agitation–Sedation Scale: validity and reliability in adult intensive care unit patients." *American journal of respiratory and critical care medicine* 166.10 (2002): 1338-1344.

Substance Abuse and Mental Health Services Administration. *Medications for Opioid Use Disorder.* Treatment Improvement Protocol (TIP) Series 63, Full Document. HHS Publication No. (SMA) 19- 5063FULLDOC. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2018.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weillller E, Hergueta T, Baker R, Dunbar GC (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998; 59 (Suppl 20):22-33.

Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, Ferri M, Pastor-Barriuso R. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017 Apr; 357:j1550 http://dx.doi.org/10.1136/bmj.j1550.

Tompkins DA, Bigelow GE, Harrison JA, Johnson RE, Fudala PJ, Strain EC Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument. Drug Alcohol Depend. 2009 Nov; 105(1-2):154-9.

Vernon MK, Revicki DA, Awad AG, Dirani R, Panish J, Canuso CM, Grinspan A, Mannix S, Kalali AH. Psychometric evaluation of the Medication Satisfaction Questionnaire (MSQ) to

assess satisfaction with antipsychotic medication among schizophrenia patients. Schizophrenia Res. 2010 May;118(1-3):271-8.

Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003 Apr-Jun; 35(2):253-9.

22 APPENDICES

22.1 Appendix 1 –Schedule of Events – Visit 1 (In ED, inpatient unit or Outpatient Clinic within 7 days (168 h) after OD

Procedure / Assessment	Screening Procedures (Visit 1)	Treatment Period (Visit 1)				
		Pre-Suboxone dose Procedures	Suboxone Dosing	Post-Suboxone dose Procedures	Sublocade Dosing	Post-Sublocade dose Procedures
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Demographics	X					
Medical History	X					
Brief Physical Examination	X					
Concomitant Medications Assessment	X					
Vital Signs	X					
Height/Weight/BMI	X					
Breathalyzer	X					
Urine Pregnancy Test	X[b]					
DSM-5 OUD/AUD/SUD Checklist	X					
Liver function laboratory tests (STAT)		X[d]				
COWS		X[e]		X		X
OC-VAS		X[e]		X		
Delay Discounting Task		X		X		
Opioid Demand Task		X		X		
SUBOXONE Test Dose			X[f,g]			
SUBLOCADE Dose					X	
PGx Sampling				X[a]		
AE Assessment		X		X[g]		X
Clinic appointment visit scheduled for next dose						X

AE = adverse event; COWS = Clinical Opiate Withdrawal Scale; MINI = Mini-International Neuropsychiatric Interview

a. PGx samples will only be taken from subjects that consent to participate in the optional PGx sub-study.
b. Urine pregnancy test, only for females of child-bearing potential. Results must be available and reviewed prior to Suboxone treatment.
c. Subjects will be included in the study only after it is determined that subject meets all inclusion criteria and none of the exclusion criteria.
d. STAT Local labs will be used for screening liver function tests. Samples must be drawn prior to dosing and will include ALT, AST and bilirubin. Abnormal liver function tests (LFTs) will be followed at clinic visits according to investigator's judgement. Liver function tests obtained for clinical reasons will also be used for research purposes if we are unable to obtain blood for research purposes. An etiological evaluation will be performed if a hepatic adverse event is suspected.
e. The COWS and OC-VAS will be completed after consent but prior to first administration of SUBOXONE sublingual film.
f. Day 1 SUBOXONE/SUBLOCADE Regimen includes supervised administration of 4mg/1 mg SUBOXONE sublingual film, followed by 300 mg SUBLOCADE administration.
g. Subjects will be assessed for adverse events predose and 1-2 hours postdose depending on RASS score prior to discharge.

22.2 Appendix 2 – Treatment Clinic Schedule of Events – (Week 1 Day 2 – Week 25 Day 169)

Procedure / Assessment	Treatment Period									
	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
	Wk 1 D 2 (-0/+3) D	Wk 2 D 8 (-0/+4) D	Wk 3 D 15 ±4 D	Wk 4 D22 (±4) D	Wk 5 D29 (±4) D	Wk 6 D36 (-2/+4) D	Wk 7 D43 (±4) D	Wk 8 D50 (±4) D	Wk 9 D57 (±4) D	Wk 10 D64 (-2/+4) D
Counselling	X	X	X	X	X	X	X	X	X	X
Urine Drug Screen	X	X	X	X	X	X	X	X	X	X
COWS	X	X	X	X	X	X	X	X	X	X
MINI International Neuropsychiatric Interview	X									
Delay Discounting Task	X									
Opioid Demand Task	X									
OC-VAS[a]	X	X	X	X	X	X	X	X	X	X
TEA	X		X							
HCRUQ	X		X				X			
MSQ	X		X							
WPAI:SHP	X									
AE Assessment	X	X	X	X	X	X	X	X	X	X
Concomitant Medications Assessment	X	X	X	X	X	X	X	X	X	X
Brief Physical Examination	X									
Vital Signs	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[b]	X	X	X	X	X	X	X	X	X	X
SUBLOCADE Injection		X				X				X
Liver function lab tests	X				X				X	
Laboratory Tests	X									

HCRUQ = Health Care Resource Utilization Questionnaire; WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

a. OC-VAS will be assessed prior to SUBLOCADE injection
b. Urine pregnancy test, only for females of child-bearing potential. Results will be obtained prior to SUBLOCADE injection.

Appendix 2 - Treatment Clinic Schedule of Events – (Week 1 Day 2 – Week 25 Day 169)

Procedure / Assessment	**Treatment Period**									
	Visit 12	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19**	**End of Treatment / Early Term**	**30-Day Safety Follow-up Telephone Call[d]**
	Wk 11 D 71 (±4) D	**Wk 12 D 78 (±4) D**	**Wk 13 D 85 (±4) D**	**Wk 14 D92 (-2/+4) D**	**Wk 16 D106 (±4) D**	**Wk 18 D120 (-2/+4 D**	**Wk 20 D134 (±4) D**	**Wk 22 D148 (-2/+4) D**	**Wk 25 D 169 (±4) D**	**Wk 29 Day 199 (±4) D**
Counselling	X	X	X	X	X	X	X	X	X	
Urine Drug Screen	X	X	X	X	X	X	X	X	X	
Delay Discounting Task		X							X	
Opioid Demand Task		X							X	
OC-VAS[a]	X	X	X	X	X	X	X	X	X	
COWS	X	X	X	X	X	X	X	X	X	
TEA	X					X			X	
HCRUQ	X			X		X		X	X	
MSQ	X					X			X	
Employment Question	X					X			X	X footnote
AE Assessment	X	X	X	X	X	X	X	X	X	X
Concomitant Medications Assessment	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	
Urine Pregnancy Test[b]	X	X	X	X	X	X	X	X	X	X
SUBLOCADE Injection				X		X		X		
Liver function laboratory testing			X				X		X	

a. OC-VAS will be assessed prior to SUBLOCADE injection
b. Urine pregnancy test, only for females of child-bearing potential. Results will be obtained prior to SUBLOCADE injection.
c. All subjects will receive a safety follow-up telephone call 30 days after their EOT/ET visit to assess AEs, SAEs, pregnancy status (if applicable) and concomitant medications. Subjects who decline to continue in MAT will receive monthly safety follow-up phone calls for an additional 5 months (6 months total) to assess SAEs, pregnancy status (if applicable) and concomitant medications.

22.3 Appendix 3 – Liver Safety

Monthly monitoring of liver chemistry will occur during the study treatment period. The following should occur if a subject meets any of the liver chemistry stopping criteria as outlined in Section 6.4.5 of [redacted] of the protocol:

- Subject should immediately be withdrawn from treatment. Do not re-challenge with study treatment.
- Completed the "Safety Follow-up Procedures" listed below.
- Upon completion of the safety follow-up, the subject must be withdrawn from the study unless further follow-up is required.

Subjects with ALT > 3x ULN and bilirubin > 2x ULN (> 35% direct); or ALT > 3x ULN and INR > 1.5:

- **This event is an SAE** and should be reported using the SAE Reporting Form (reference Section 11.2. Serum bilirubin fractionation should be performed, if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).

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

- Make every reasonable attempt to have the subject return to the clinic within 24 hours for repeat liver chemistries, additional testing and close monitoring (with specialist or hepatology consultation recommended).
- Monitor the subject twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Subjects with ALT > 5x ULN or ALT > 3x ULN who have hepatitis symptoms or rash, cannot be monitored for 4 weeks or have elevations that persist ≥ 4 weeks:

- Make every reasonable attempt to have the subject return to the clinic within 24-72 hours for repeat liver chemistries and additional testing.
- Monitor subject weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Subjects with ALT > 3x ULN and < 5x ULN and bilirubin < 2x ULN, who do not exhibit hepatitis symptoms or rash:

- Subject may continue study treatment, if liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) can be monitored weekly for up to 4 weeks.

- If the subject later meets the liver chemistry stopping criteria (outlined in Section 6.4.5 of the protocol), immediately withdraw study treatment, perform additional testing and continue safety follow-up until liver chemistries resolve, stabilize or return to baseline values.

- After 4 weeks of monitoring, if ALT < 3x ULN and bilirubin < 2x ULN, subject must be monitored twice monthly until liver chemistries normalize or return to within baseline values.

Additional follow-up procedures for subjects who meet any of the liver safety stopping criteria:

- Viral hepatitis serology including:

    - Hepatitis A Immunoglobulin M (IgM) antibody,

    - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM),

    - Hepatitis C RNA,

    - Cytomegalovirus IgM antibody,

    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing), and

    - Hepatitis E IgM antibody.

    - Blood sample for PK analysis, obtained within 48 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw in the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated or a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are outlined in the laboratory manual.

    - Serum creatine phosphokinase and lactate dehydrogenase.

    - Fractionate bilirubin, if total bilirubin > 2x ULN.

    - Assess eosinophilia.

    - Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) as relevant on the AE eCRF.

- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications eCRF.

- Record alcohol use in the eCRF.

- **In addition, the following are required for subjects with ALT > 3x ULN and bilirubin > 2x ULN (< 35% direct) but optional for other abnormal liver chemistries**:

    - Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).

    - Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to livery injury in subjects with definite or likely acetaminophen use in the preceding week [James 2009]).

    - Liver imaging (ultrasound, MRI, or CT) to evaluate liver disease. Data should be entered into the eCRF, if these tests are performed.