Study Protocol

NCT03993392

Study Number: INDV-6000-403

Title: An Open-label, Rapid Initiation Study for Extended-Release Buprenorphine Subcutaneous Injection (SUBLOCADE™)

Protocol Date: 14 August 2019

16.1.1 CLINICAL RESEARCH PROTOCOL

DRUG:	SUBLOCADE™ (extended-release buprenorphine)
STUDY NUMBER:	INDV-6000-403
PROTOCOL TITLE:	An Open-label, Rapid Initiation Study for Extended-Release Buprenorphine Subcutaneous Injection (SUBLOCADE™)
SHORT TITLE:	SUBLOCADE Rapid Initiation Study
IND NUMBER:	107,607
SPONSOR:	Indivior Inc. 10710 Midlothian Turnpike, Suite 125 North Chesterfield, VA 23235 USA
ORIGINAL PROTOCOL DATE:	11 July 2019
AMENDMENT 1 PROTOCOL DATE:	14 August 2019

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: An Open-label, Rapid Initiation Study for Extended-Release Buprenorphine Subcutaneous Injection (SUBLOCADE™)

Study No: INDV-6000-403

Amendment 1 Protocol Date: 14 August 2019

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

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practice (GCP) as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

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

Signed: [redacted] Date: 15-Aug-2019
DD-MMM-YYYY

Indivior Medical Monitor
Indivior Inc.

Signed: [redacted] Date: 14 Aug 2019
DD-MMM-YYYY

Senior Vice President, Global Medicines Development
Indivior Inc.

INDV-6000-403 - AN OPEN-LABEL, RAPID INITIATION STUDY FOR EXTENDED-RELEASE BUPRENORPHINE SUBCUTANEOUS INJECTION (SUBLOCADE™)

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to SUBLOCADE™ (extended-release buprenorphine) are the confidential and proprietary information of Indivior Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Indivior Inc.

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. 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, and other study-related materials, and are qualified to perform their delegated tasks. I will provide all study personnel copies of the protocol and any amendments and grant access to all information provided by Indivior or specified designees. I will discuss the material with them to ensure that they are fully informed about study drugs and appropriate information throughout the study. Mechanisms are in place to ensure that clinic staff receives the appropriate information throughout the study.

Signed: [redacted] Date: 16/AUG/2019
DD-MMM-YYYY

Printed Name and Credentials:	[redacted]
Title:	[redacted]
Clinic Name:	[redacted]
Telephone:	[redacted]
Address:	[redacted]

SUMMARY OF CHANGES

	Change	Section Affected	Summary of Change(s)
1.	Additional COWS and OC-VAS	Table 2	Increased frequency, resulting in additional assessments at 2, 3, 6, 16 and 20 hr.
2.	Additional Sedation VAS	Table 2	Increased frequency, resulting in additional assessments at 16 and 20 hr.
3.	Additional Endpoints added and all listed as "Key Endpoints"	Section 3.1 Section 14.4.1	Number and percentage of subjects with ≥ 6 point increase in COWS within first 6, 12, 24, or 48 hours post SUBLOCADE administration. Area under the curve (AUC) of COWS score from the time of administration of SUBLOCADE (i.e., time 0) through 6, 12, 24 and 48 hours after SUBLOCADE administration.
4.	Definition of an AE	Section 10	Attempted depot removal to be recorded as an AE
5.	Sample Size	Section 14.2	Added information for a true event rate of 1% to Table 4.
6.	Full Analysis Set (FAS) Definition	Section 14.3.1	Updated FAS definition to align with timepoints up to 48 hours for the additional key endpoints.
7.	Missing Data	Section 14.7	Added section to address handling of missing data in the statistical analysis.

STUDY PERSONNEL INFORMATION

Medical Monitor: (24-hour coverage)	[redacted]
Back-up Medical Monitor	[redacted]

STUDY SUMMARY

Protocol Number: INDV-6000-403

Title: An Open-label, Rapid Initiation Study for Extended-Release Buprenorphine Subcutaneous Injection (SUBLOCADE™)

Rationale: Currently, patients who are appropriate candidates for SUBLOCADE™ (buprenorphine extended-release) injection for subcutaneous use must initiate treatment with transmucosal (TM) buprenorphine for a minimum of 7 days before receiving their first injection of SUBLOCADE. This study is to evaluate the safety and tolerability of starting SUBLOCADE treatment following a shorter period of TM buprenorphine treatment.

Study RB-US-11-0020 previously evaluated subjects receiving TM buprenorphine for 7 days before being administered 100 mg SUBLOCADE, as well as subjects receiving 50 mg, 100 mg or 200 mg SUBLOCADE with no TM buprenorphine initiation. The number of treatment-emergent adverse events (TEAE) reported for each group was comparable, with no serious adverse events (SAE) related to study drug and no adverse events (AE) leading to discontinuation. In addition, there was no increase in the Clinical Opiate Withdrawal Scale (COWS) scores across groups. The study demonstrated that there were no safety or tolerability issues when SUBLOCADE was administered without initiating treatment with TM buprenorphine.

This present study will ensure that subjects provide a history of last opioid agonist use (short-acting and long-acting) and are experiencing at least mild withdrawal before administration of 4 mg TM buprenorphine. If no evidence of intolerability or precipitated withdrawal is observed after 1 hour, subjects will be administered a single injection of 300 mg SUBLOCADE. Following the injection, subjects will remain in the clinic for approximately 48 hours and will be assessed for safety and tolerability, as well as for any signs of precipitated withdrawal.

	This study will also characterise the peak and overall plasma exposure to N-methyl-2-pyrrolidone (NMP), the biocompatible solvent used in the SUBLOCADE formulation, following a single SC injection of 300 mg SUBLOCADE.
Target Population:	Adult subjects with moderate to severe opioid use disorder (OUD) as assessed by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria, who are not currently treated with buprenorphine.
Number of Subjects:	Sufficient subjects will be enrolled to ensure that 15 subjects receive SUBLOCADE and are evaluable for precipitated withdrawal; that is, 15 subjects having data for at least 1 COWS assessment before SUBLOCADE injection and COWS assessments for 48 hours after SUBLOCADE injection.
Objective:	The objective of this study is to evaluate the safety and tolerability of initiating SUBLOCADE following a single dose of TM buprenorphine.
Study Design:	Subjects who provide written informed consent will enter a Screening Period to confirm study eligibility. Eligible subjects will be advised to abstain from short-acting opioids (such as morphine sulfate, oxycodone, hydromorphone, oxymorphone or codeine) for at least 6 hours and long-acting opioids (such as methadone or levorphanol) for 24 hours before arriving at the clinic on the morning of Day 1 (American Society of Addiction Medicine [ASAM] 2015, Buvidal 2018). Eligible subjects will be informed that under-reporting of the last use of opioids puts him/her at higher risk for rapid and intense onset of withdrawal symptoms. Eligible subjects will also be advised to abstain from alcohol before checking into the clinic. Upon arriving at the clinic on the morning of Day 1, subjects will provide a urine sample for a urine drug screen (UDS) for qualitative and quantitative analysis and complete an alcohol breathalyser test. The Investigator will discuss any positive UDS reports with the subject and will ask him/her to self-report recent illicit drug use (including the use of a TimeLine Follow Back [TLFB]). Subjects who indicate that they have used long-acting opioids within 24 hours, or

who have a blood alcohol concentration (per breathalyser) of concern to the Investigator, will not be permitted to check in and may be re-scheduled for check-in within the Screening Period. Subjects who report having used short-acting opioids within 6 hours may be permitted to check in at the discretion of the Investigator.

All subjects will have their concomitant medications since screening reviewed to ensure no contraindicated medications have been used within the permitted window. Female subjects of childbearing potential will also perform a urine pregnancy test. A female with a positive pregnancy test prior to enrolment will be a screen failure.

A subject will then be assessed for withdrawal symptoms using a COWS and for craving using the Opioid Craving Visual Analogue Scale (OC-VAS).

If the subject's COWS is ≥8, the subject will also complete the remaining pre-buprenorphine assessments including: vital signs, 12-lead electrocardiograms (ECG), AEs, and sedation using a Sedation VAS. Body weight and a blood sample for liver function testing (LFT) will also be collected at any time before dosing with SUBLOCADE.

If a subject's COWS is not ≥8, the subject may either be re-scheduled for check-in within the Screening Period or remain in the clinic (at the Investigator's discretion), and the COWS may be repeated until the subject achieves a score ≥8. Only when the COWS is ≥8 and all pre-buprenorphine assessments have been completed may the subject receive TM buprenorphine.

One hour after the 4 mg TM buprenorphine dose, the subject will complete pre-SUBLOCADE assessments including: COWS (first, to assess precipitated withdrawal after TM buprenorphine) and OC-VAS, then Sedation VAS, AEs, vital signs and concomitant medications.

Subjects experiencing precipitated withdrawal will be treated for withdrawal symptoms. If precipitated withdrawal occurs, the TM induction may be restarted later on the same day at the discretion of the Investigator, based on the half-life of the opioid reported on the TLFB. Alternatively, the Investigator may permit the subject to return

to the facility on another day (within the Screening Period). Returning subjects will repeat all Day 1 scheduled assessments.

If the subject experiences withdrawal symptoms at any time, he/she may be treated symptomatically (SAMHSA TIP 63 2018):

- nausea: ondansetron or metoclopramide
- diarrhoea: loperamide
- anxiety, irritability, sweating: clonidine
- insomnia: diphenhydramine, trazodone
- pain: nonsteroidal anti-inflammatory drugs

If the subject does not display any allergic/hypersensitivity reaction or clinical signs of sedation, and does not experience precipitated withdrawal, 300 mg SUBLOCADE may be administered to the subject. A blood sample will be collected prior to SUBLOCADE administration for NMP PK assessment.

Following SUBLOCADE (300 mg) administration, the subject will remain in the clinic for approximately 48 hours and will be assessed for safety and tolerability, as well as for any signs of precipitated withdrawal.

Blood samples for NMP PK assessment will be collected as close to the nominal timepoint as possible. In addition, subjects will be assessed for the following: AEs, vital signs, 12-lead ECGs and concomitant medications. Subjects will also be examined for withdrawal symptoms within 48 hours of SUBLOCADE administration based on COWS, opioid craving (using OC-VAS), and sedation (using Sedation VAS). The injection site will also be assessed for any signs of reaction or infection, which will be reported as AEs if present.

Subjects who experience opioid withdrawal after SUBLOCADE administration may be treated with non-opioid medications as above (SAMHSA, TIP 63 2018). Supplemental TM buprenorphine (after SUBLOCADE administration) may only be permitted after discussions with the medical monitor. Subjects will not be discontinued from treatment due to illicit opioid use (including buprenorphine).

Subjects will return to the clinic weekly, until the end-of-treatment (EOT) visit, to assess COWS, OC-VAS, AEs, vital signs and concomitant medications; the injection site will be reviewed for any evidence of tampering and for any signs of reaction or infection. Subjects will also self-report their illicit drug use since last visit, including a TLFB, and provide a urine sample for UDS. A blood sample for NMP PK assessment and a blood sample for LFTs will be collected. If LFT value increases are noted, additional testing may be performed at the discretion of the Investigator.

All subjects will receive counselling as determined by local standard of care throughout the study from Day 1 through EOT (Day 29).

All subjects who receive SUBLOCADE (including those who wish to discontinue early), will be encouraged to attend the EOT visit 28 days after SUBLOCADE administration (Day 29). After enrolment, available treatment options for completed subjects will be discussed. Any subject with ongoing AEs or concomitant medications at the EOT and has not continued medication for OUD (MOUD) will also be followed up by phone 2 weeks later for the End of Study (EOS) visit (Day 43) to assess the ongoing AEs or concomitant medications only.

Subjects who discontinue from the study before TM buprenorphine administration will be considered screen failures and will not be required to complete an EOT visit.

Subjects who discontinue from the study after TM buprenorphine administration, and before SUBLOCADE administration, will not be required to complete an EOT visit and will be contacted via telephone 24 to 72 hours after TM buprenorphine administration to assess any ongoing AEs and concomitant medications only.

Key Endpoints:	Number and percentage of subjects who experience any precipitated withdrawal within approximately 1 hour after SUBLOCADE administration (defined as an increase in COWS by ≥6 from the pre-SUBLOCADE value). Number and percentage of subjects with ≥ 6 point-increase in COWS within the first 6, 12, 24, or 48 hours post SUBLOCADE administration. Area under the curve (AUC) of COWS score from the time of administration of SUBLOCADE (i.e., time 0) through 6, 12, 24 and 48 hours after SUBLOCADE administration. Total score on the COWS during the treatment period (i.e. at each assessment timepoint from administration of TM buprenorphine at Day 1 through EOT) Score on the OC-VAS during the treatment period
Exploratory Endpoints:	Number and percentage of subjects who experience precipitated withdrawal from TM buprenorphine (defined as an increase in COWS by ≥6 from prior to the most recent dose of TM buprenorphine before SUBLOCADE administration). Peak and overall plasma exposure to NMP following a single SC injection of 300 mg SUBLOCADE.
Other Safety Assessments:	Major safety endpoints will include the proportion of subjects with TEAEs of the following types at any time during the treatment period (i.e., any time after administration of TM buprenorphine): TEAE, drug-related TEAE, serious TEAE, drug-related serious TEAE and TEAE leading to treatment discontinuation. Additional safety endpoints will include assessment of laboratory results, vital signs and concomitant medications. Withdrawal symptoms will be monitored by COWS (secondary endpoint), opioid craving (using OC-VAS; secondary endpoint), sedation (using Sedation VAS) and AEs.

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASAM	American Society of Addiction Medicine
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BUP	Buprenorphine
CI	confidence interval
cm	centimetre
CNS	central nervous system
COWS	Clinical Opiate Withdrawal Scale
CYP	cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
ET	early termination
FAS	full analysis set
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

GMP	Good Manufacturing Practice
Hep	Hepatitis
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
kg	Kilogram
LD	lactase dehydrogenase
LFT	liver function test(ing)
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
Min	Minute
mm	Millimetre
MOUD	Medication for Opioid Use Disorder
msec	Millisecond
NCS	Not clinically significant
NNRTI	non-nucleoside reverse transcriptase inhibitor
NMP	N-methyl-2-pyrrolidone
OC-VAS	opioid craving visual analogue scale
OUD	opioid use disorder
PK	pharmacokinetic(s)

PLGH	poly(DL-lactide-co-glycolide) with a carboxylic acid end group
QA	quality assurance
QTcF	corrected QT – Fridericia's
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TLFB	TimeLine Follow Back
TM	Transmucosal
UDS	urine drug screen
ULN	upper limit of normal
USPI	United States Prescribing Information
WBC	White blood cell
WHO	World Health Organization
VAS	visual analogue scale

1 INTRODUCTION AND RATIONALE

1.1 Background

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

SUBLOCADE™ (extended-release buprenorphine) injection, for subcutaneous (SC) use (CIII) is an extended-release formulation of buprenorphine, a mu-opioid receptor partial agonist. SUBLOCADE is administered once monthly by SC injection and provides sustained plasma levels of buprenorphine over the dosing interval. SUBLOCADE uses buprenorphine and the ATRIGEL® Delivery System, which consists of a biodegradable polymer poly (DL-lactide-co-glycolide) with a carboxylic acid end group (PLGH), dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). SUBLOCADE is injected as a solution, and subsequent precipitation of the polymer creates a solid depot containing the buprenorphine. After initial formation of the depot, buprenorphine is released via diffusion from, and the biodegradation of, the depot.

SUBLOCADE is currently indicated for the treatment of moderate to severe OUD in patients who have initiated treatment with a transmucosal (TM) buprenorphine-containing product to suppress opioid withdrawal signs and symptoms for a minimum of 7 days (SUBLOCADE United States Prescribing Information [USPI]). SUBLOCADE should be used as a part of a complete treatment program that includes counselling.

The recommended dose of SUBLOCADE is 300 mg monthly for the first 2 months followed by monthly 100-mg maintenance doses; increasing the monthly maintenance dose to 300 mg may be considered for patients who tolerate the 100-mg dose, but do not demonstrate a satisfactory clinical response, as evidenced by self-reported illicit opioid use or urine drug screen (UDS) positive for illicit opioid use.

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

1.2 Study Rationale

Currently, patients who are appropriate candidates for SUBLOCADE must initiate treatment with TM buprenorphine for a minimum of 7 days before receiving their first

injection of SUBLOCADE. This study is to evaluate the safety and tolerability of starting SUBLOCADE treatment following a shorter period of TM buprenorphine treatment.

Study RB-US-11-0020 previously evaluated subjects receiving TM buprenorphine for 7 days before being administered 100 mg SUBLOCADE, as well as subjects receiving 50 mg, 100 mg or 200 mg SUBLOCADE with no TM buprenorphine initiation. The number of treatment-emergent adverse events (TEAE) reported for each group was comparable, with no serious adverse events (SAE) related to study drug and no adverse events (AE) leading to discontinuation. In addition, there was no increase in the Clinical Opiate Withdrawal Scale (COWS) scores across groups. The study demonstrated that there were no safety or tolerability issues when SUBLOCADE was administered without initiating treatment with TM buprenorphine.

This present study will ensure that subjects provide a history of last opioid agonist use (short-acting and long-acting) and are experiencing at least mild withdrawal before administration of 4 mg TM buprenorphine. If no evidence of intolerability or precipitated withdrawal is observed after 1 hour, subjects will be administered a single injection of 300 mg SUBLOCADE.

Following the injection, subjects will remain in the clinic for approximately 48 hours and will be assessed for safety and tolerability, as well as for any signs of precipitated withdrawal.

This study will also characterize the peak and overall plasma exposure to NMP, the biocompatible solvent used in SUBLOCADE formulation, following single SC injection of 300 mg SUBLOCADE. The pharmacokinetics (PK) of NMP following SC injection of ATRIGEL has been investigated in animal studies (rat, rabbit). However, no NMP PK data have been generated in human subjects following administration of SUBLOCADE.

1.2.1 Pharmacokinetics

The PK of buprenorphine following SC injection of SUBLOCADE was evaluated in subjects with OUD after single doses (50 mg to 200 mg) and repeated doses (50 to 300 mg) separated by 28 days for up to 12 injections (SUBLOCADE USPI). After SUBLOCADE injection, an initial buprenorphine peak was observed and the median time to maximum concentration occurred at 24 hours after injection. After the initial buprenorphine peak, the plasma buprenorphine concentrations decreased slowly to a plateau. Steady-state was achieved at 4 to 6 months.

1.2.2 Preclinical Pharmacology

See SUBLOCADE USPI.

1.2.3 Potential for Drug-Drug Interactions

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome P450 (CYP)3A4; therefore, potential interactions may occur when SUBLOCADE is given concurrently with agents that affect CYP3A4 activity (SUBLOCADE USPI). The effects of co-administered CYP3A4 inducers or inhibitors have been established in studies using transmucosal buprenorphine. Patients who transfer to SUBLOCADE treatment from a regimen of TM buprenorphine used concomitantly with CYP3A4 inhibitors (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), human immunodeficiency virus (HIV) protease inhibitors or CYP3A4 inducers (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) should be monitored to ensure that the plasma buprenorphine level provided by SUBLOCADE is adequate and not excessive. Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in in vitro studies using human liver microsomes. However, the plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic SUBLOCADE doses are not expected to significantly affect metabolism of other co-medications.

1.2.4 Clinical Adverse Event Profile

The systemic safety profile for SUBLOCADE, given by a healthcare provider in clinical studies, was consistent with the known safety profile of TM buprenorphine with the expected exception of injection site reactions. In double-blind, placebo-controlled study RB-US-13-0001 (NCT02357901), subjects receiving SUBLOCADE 300/300 mg (6 doses of 300 mg SC injections), 300/100 mg (300 mg SC injections for the first 2 doses followed by 4 doses of 100 mg SC injections), and placebo (volume-matched ATRIGEL® delivery system subcutaneous injections) experienced the following common non-injection site reaction adverse reactions: constipation, nausea, vomiting, abnormal liver enzymes, headache, sedation and somnolence. Most SUBLOCADE injection site adverse drug reactions were of mild to moderate severity, with 1 report of severe injection site pruritus. None of the injection site reactions were serious. One reaction, an injection site ulcer, led to study treatment discontinuation.

Adverse events led to premature discontinuation in 4% of the group receiving SUBLOCADE compared with 2% in the placebo group (RB-US-13-0001).

In the Phase 3 open-label study (RB-US-13-0003, NCT02510014), subjects were permitted to remain on the 300 mg SUBLOCADE and AEs leading to drug dose reduction (to 100 mg) were reported in 7.3% of all subjects.

1.2.5 Elevations in Liver Function Tests

The SUBLOCADE USPI states that dose-dependent hepatic effects observed in the Phase 3, double-blind study RB-US-13-0001 included the incidence of alanine aminotransferase (ALT) more than 3 times the upper limit of normal (>3 × ULN) in 12.4%, 5.4% and 4.0%

of the SUBLOCADE 300/300-mg, SUBLOCADE 300/100-mg and placebo groups, respectively. The incidence of aspartate aminotransferase (AST) >3 × ULN was 11.4%, 7.9% and 1.0%, respectively.

Additional exposure-response analyses were conducted to evaluate the relationship between buprenorphine plasma concentration and the probability of elevations of ALT and AST (> 3× ULN, >5× ULN, and > 8× ULN). Overall, exposure-response curves were flat within the observed concentration range.

1.2.6 Potential Risk to Foetal Development

See SUBLOCADE USPI.

1.2.7 Dosing Regimen

The recommended initial dose of SUBLOCADE is 300 mg (SUBLOCADE USPI).

Given that the maximum plasma concentration of SUBLOCADE is achieved 24 hours after the first injection, in-clinic assessment of withdrawal symptoms and other symptoms (e.g., injection site reactions, sedation, vital signs change) within the first 48 hours was deemed appropriate.

The single dose of TM buprenorphine was selected for rapid initiation of SUBLOCADE as one 4-mg dose should be a sufficient dose to exclude hypersensitivity and precipitated withdrawal in subjects who have recently used opioids.

1.3 Risk-Benefit Assessment

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

1.3.1 Risk Assessment

The safety profile of buprenorphine is well-established, and the AE profile of buprenorphine is well characterised. Commonly reported AEs include drug withdrawal syndrome, constipation, headache, nausea and vomiting. Buprenorphine has been approved for multiple indications and routes of administration (e.g., TM, buccal, intramuscular, intravenous, transdermal, rectal and subdermal) in multiple countries and by various manufacturers. Buprenorphine has also been approved as a monthly SC injection for the treatment of OUD (SUBLOCADE USPI).

The most common adverse drug reactions 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, none were serious, and they decreased in frequency with subsequent injections. There were no unexpected safety findings. The safety profile of SUBLOCADE observed in the Phase III studies was generally consistent with the known safety profile of buprenorphine, with the expected exception of injection site tolerability and reaction.

Subjects in the study will have their first SUBLOCADE injection following a minimal period of treatment with TM buprenorphine which is supported by data from development study (RB-US-11-0020). However, subjects for the study will be treatment-seeking and still using illicit opioids which puts them at risk of a precipitated withdrawal if buprenorphine is administered too soon after their last use of a full opioid agonist. Specifically, SUBLOCADE may lead to a prolonged withdrawal state given the exposure reached after a 300-mg injection and the extended period of buprenorphine exposure. This risk is mitigated by the requirement for subjects to be in withdrawal (COWS ≥8) prior to receiving TM buprenorphine. Waiting 1 hour following the administration of TM buprenorphine also permits observation of any allergic/hypersensitivity reaction to buprenorphine before the injection is administered. These measures should provide adequate opportunity to observe buprenorphine-related safety responses, including precipitated withdrawal (as a result of the subject inadequately/incorrectly reporting use of long- or short-acting opioids) prior to a subject receiving SUBLOCADE.

1.3.2 Benefit Assessment

Clear efficacy was demonstrated both in the pivotal and in additional supporting studies of the SUBLOCADE clinical development programme (SUBLOCADE USPI).While they will receive limited benefit from participation in this single-dose (of SUBLOCADE) study, results from this investigation could lead to more rapid SUBLOCADE initiation, which is expected to improve treatment compliance, engagement and retention. With increasing amounts of fentanyl contamination of the heroin drug supply, it is also important to treat patients with a medicine that can protect them from overdose as soon as they are willing to engage in treatment. Recently reported data (Wiest 2019) supports that buprenorphine, administered at doses resulting in consistent plasma levels of 2ng/mL and 5ng/mL (similar to the concentrations resulting from both labelled doses of SUBLOCADE), is able to inhibit fentanyl-induced respiratory depression. Being able to initiate treatment-seeking patients with SUBLOCADE on the 1st day of treatment therefore helps to protect patients when they are most vulnerable.

1.3.3 Overall Risk-Benefit Summary

Taken together, these findings indicate a favourable benefit/risk assessment for this study to evaluate a faster treatment initiation protocol for SUBLOCADE in patients with OUD.

2 STUDY OBJECTIVES

The objective of this study is to evaluate the safety and tolerability of initiating SUBLOCADE following a single dose of TM buprenorphine.

3 STUDY ENDPOINTS

3.1 Key Endpoints

- Number and percentage of subjects who experience any precipitated withdrawal within approximately 1 hour after SUBLOCADE administration (defined as an increase in COWS by ≥6 from the pre-SUBLOCADE value).
- Number and percentage of subjects with ≥ 6-point increase in COWS within the first 6, 12, 24, or 48 hours post SUBLOCADE administration.
- Area under the curve (AUC) of COWS score from the time of administration of SUBLOCADE (i.e., time 0) through 6, 12, 24 and 48 hours after SUBLOCADE administration.
- Total score on the COWS during the treatment period (i.e. at each assessment timepoint from administration of TM buprenorphine at Day 1 through EOT).
- Score on the opioid craving visual analogue scale (OC-VAS) during the treatment period.

3.2 Exploratory Endpoints

The exploratory endpoints are the following:

- Number and percentage of subjects who experience precipitated withdrawal from TM buprenorphine (defined as an increase in COWS by ≥6 from prior to the most recent dose of TM buprenorphine before SUBLOCADE administration).
- Peak and overall plasma exposure to NMP following a single SC injection of 300 mg SUBLOCADE.

3.3 Other Safety Assessments

Major safety endpoints will include the proportion of subjects with TEAEs of the following types at any time during the treatment period (i.e., any time after administration of TM buprenorphine): TEAE, drug-related TEAE, serious TEAE, drug-related serious TEAE and TEAE leading to treatment discontinuation.

Additional safety endpoints will include assessment of laboratory results, vital signs and concomitant medications.

Withdrawal symptoms will be monitored by COWS (secondary endpoint), AEs, opioid craving (using OC-VAS; secondary endpoint) and sedation (using Sedation VAS).

4 STUDY PLAN

4.1 Study Design

Subjects who provide written informed consent will enter a Screening Period to confirm study eligibility. During screening, human immunodeficiency virus (HIV-1/HIV-2) and hepatitis (Hep B and Hep C Antibody) testing is only required to be performed in the absence of a positive (documented) medical history of these conditions.

Eligible subjects will be advised to abstain from short-acting opioids (such as morphine sulfate, oxycodone, hydromorphone, oxymorphone or codeine) for at least 6 hours and long-acting opioids (such as methadone or levorphanol) for 24 hours before arriving at the clinic on the morning of Day 1 (American Society of Addiction Medicine [ASAM] 2015, Buvidal 2018). Eligible subjects will be informed that under-reporting of the last use of opioids puts him/her at higher risk for rapid and intense onset of withdrawal symptoms. Eligible subjects will also be advised to abstain from alcohol before checking into the clinic.

Upon arriving at the clinic on the morning of Day 1, eligible subjects will provide a urine sample for a UDS for qualitative and quantitative analysis and complete an alcohol breathalyser test. The Investigator will discuss any positive UDS reports with the subject and will ask him/her to self-report their recent illicit drug use (including the use of a TimeLine Follow Back [TLFB]).

Subjects who indicate that they have used long-acting opioids within 24 hours, or who have a blood alcohol concentration (per breathalyser) of concern to the Investigator, will not be permitted to check in and may be re-scheduled for check-in (as many times as required, but within the Screening Period). Subjects who report having used short-acting opioids within 6 hours may be permitted to check in at the discretion of the Investigator.

All subjects will have their concomitant medications since screening reviewed to ensure no contraindicated medications have been used within the permitted window. Females of childbearing potential will also perform a urine pregnancy test. A female with a positive pregnancy test prior to enrolment will be a screen failure

A subject will then be assessed for withdrawal symptoms using COWS and for craving using OC-VAS.

If the subject's COWS is ≥8, they will complete the remaining pre-buprenorphine assessments including the following: vital signs, 12-lead electrocardiograms (ECG), AEs, and sedation using a Sedation VAS. Body weight and a blood sample for liver function testing (LFT) will also be collected at any time before dosing with SUBLOCADE.

If a subject's COWS is not ≥8, the subject may either be re-scheduled for check-in within the Screening Period or remain in the clinic (at the Investigator's discretion), and the COWS may be repeated until the subject achieves a score ≥8. Only when the COWS is

≥8 and all pre-buprenorphine assessments have been completed may the subject receive TM buprenorphine.

One hour after the 4mg TM buprenorphine dose, the subject will complete pre-SUBLOCADE assessments including: COWS (first, to assess precipitated withdrawal) and OC-VAS, then Sedation VAS, AEs, vital signs and concomitant medications.

Any subject who display any allergic/hypersensitivity reaction to buprenorphine will be discontinued from the study and will be followed up via telephone call 24 to 72 hours post dose.

Subjects experiencing precipitated withdrawal will be treated for withdrawal symptoms. If precipitated withdrawal occurs before SUBLOCADE administration, the TM induction may be restarted later on the same day at the discretion of the Investigator, based on the half-life of the opioid reported on the TLFB. Alternatively, the Investigator may permit the subject to return to the facility on another day (within the Screening Period). Returning subjects will repeat all Day 1 scheduled assessments.

If the subject experiences withdrawal symptoms at any time (including precipitated withdrawal after SUBLOCADE), he/she may be treated symptomatically (SAMHSA TIP 63 2018):

- nausea: ondansetron or metoclopramide
- diarrhoea: loperamide
- anxiety, irritability, sweating: clonidine
- insomnia: diphenhydramine, trazodone
- pain: nonsteroidal anti-inflammatory drugs

If the subject does not display any allergic/hypersensitivity reaction or clinical signs of sedation, and does not experience precipitated withdrawal, 300 mg SUBLOCADE may be administered to the subject. A blood sample will be collected prior to SUBLOCADE administration for NMP PK assessment.

Sufficient subjects will be enrolled to ensure that 15 subjects are dosed with SUBLOCADE and are evaluable for precipitated withdrawal; that is, 15 subjects having data for at least 1 COWS assessment before SUBLOCADE injection and COWS assessments for 48 hours after SUBLOCADE injection.

Following SUBLOCADE (300 mg) administration, the subject will remain in the clinic for approximately 48 hours and will be assessed for safety and tolerability, as well as for any signs of precipitated withdrawal.

Blood samples for NMP PK assessment will also be collected as close to the nominal timepoint as possible. In addition, subjects will be assessed for the following: AEs, vital signs, 12-lead ECGs and concomitant medications. Subjects will also be examined for withdrawal symptoms within 48 hours of SUBLOCADE administration based on COWS,

opioid craving (using OC-VAS), and sedation (using Sedation VAS). The injection site will be assessed for signs of reaction or infection, which will be reported as AEs, if present.

Subjects who experience opioid withdrawal after SUBLOCADE administration may be treated with non-opioid medications as above (SAMHSA TIP 63 2018). Supplemental TM buprenorphine (after SUBLOCADE administration) may only be permitted after discussions with the medical monitor. Subjects will not be discontinued from treatment due to illicit opioid use (including buprenorphine).

Subjects will return to the clinic weekly, until the end-of-treatment (EOT) visit, to assess COWS, OC-VAS, AEs, vital signs and concomitant medications; the injection site will be assessed for any evidence of tampering and for any signs of reaction or infection. Subjects will also self-report their illicit drug use since last visit, including a TLFB, and provide a urine sample for UDS. A blood sample for NMP PK assessment and a blood sample for LFTs will also be collected. If LFT value increases are noted, additional testing should be performed as described in Section 8.2.7.3.

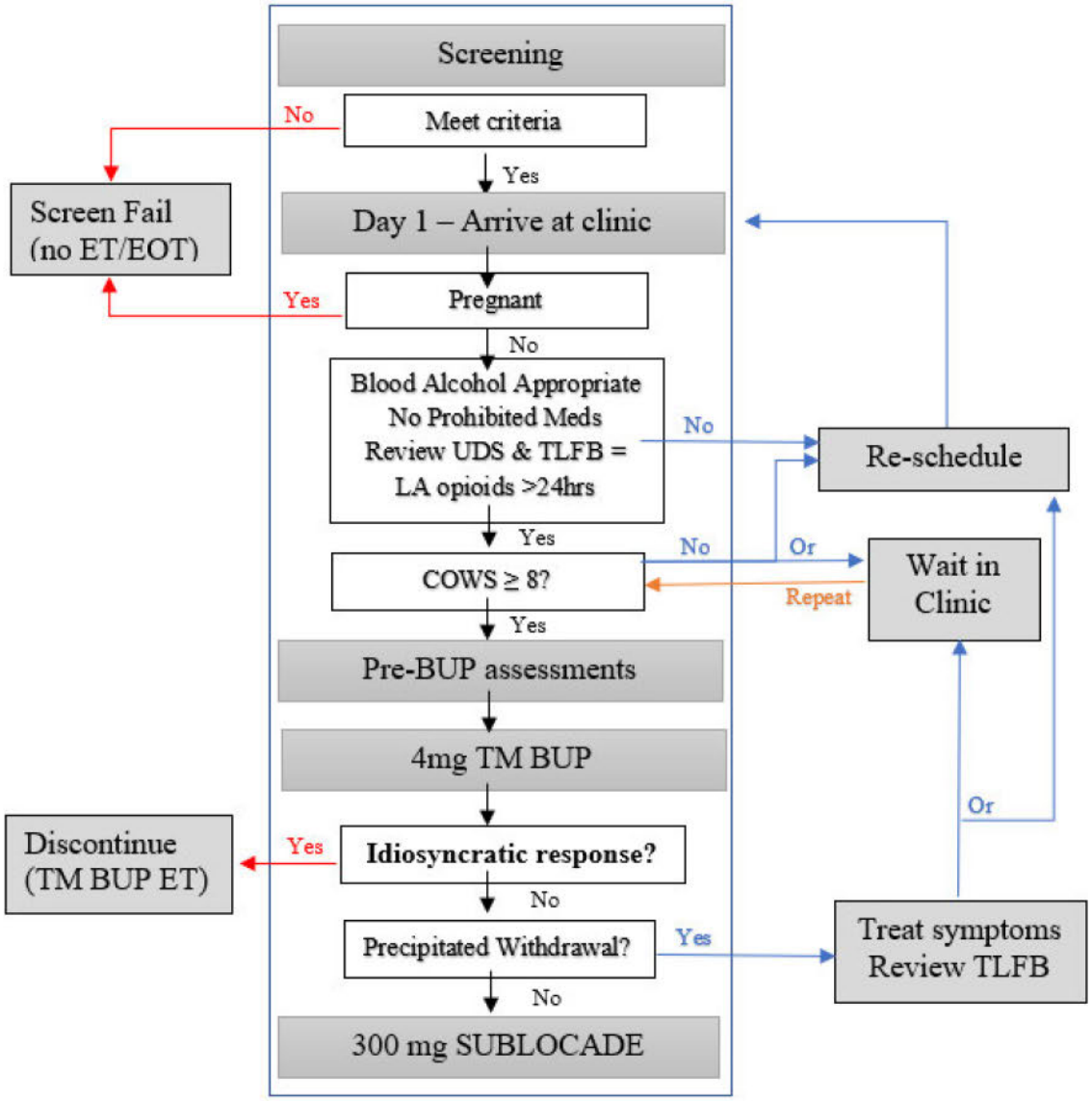
All subjects will receive counselling as determined by local standard of care throughout the study from Day 1 through EOT.

All subjects who receive SUBLOCADE (including those who wish to discontinue early), will be encouraged to attend the EOT visit 28 days after SUBLOCADE administration (Day 29). After enrolment, available treatment options for completed subjects will be discussed. Any subject with ongoing AEs or concomitant medications at the EOT and has not continued MOUD will also be followed up by phone 2 weeks later for the End of Study (EOS) visit (Day 43) to assess the ongoing AEs or concomitant medications only.

Subjects who discontinue from the study before TM buprenorphine administration will be considered screen failures and will not be required to complete an EOT visit.

Subjects who discontinue from the study after TM buprenorphine administration, and before SUBLOCADE administration, will be contacted via telephone 24 to 72 hours after TM buprenorphine administration to include assessment of AEs and concomitant medications only.

4.2 Study Schematic – Visit 2 - Injection



BUP=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; EOT=End-of-Treatment; ET=Early Termination; LA=Long-acting; TLFB = TimeLine Follow Back; TM=transmucosal; UDS=Urine Drug Screen

4.3 Schedule of Assessments

An overview of the schedule of assessments for the study overall is provided in Table 1 and the detailed schedule of assessments for the Injection Visit (Visit 2, Days 1-3) in Table 2.

Table 1 Schedule of Assessments – Overview of Study

Procedure/Assessment	**Screening**	**Injection[a]**	**1 week post dose**	**2 weeks post dose**	**3 weeks post dose**	**EOT[16]**	**EOS[17]**	**TM BUP ET[18]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Day(s)	**-30 to -1**	**1-3**	**8**	**15**	**22**	**29**	**43**	**24-72 hr Post-TM BUP dose**
Window (days)			**± 1**	**± 2**	**± 2**	**± 2**	**±5**	
Informed Consent[1]	X							
Inclusion/Exclusion Criteria	X							
Demographics	X							
Medical/Psychiatric History	X							
Substance/Drug Use History[2]	X							
Physical Examination[3]	X					X		
Height/Weight/BMI[4]	X	X[a]				X		
Vital Signs[5]	X	X[a]	X	X	X	X		
12-Lead ECG[6]	X	X[a]				X		
AE Assessment	← X →							
Concomitant Medications[7]	← X →							
HIV-1/HIV-2, Hep B, Hep C Antibody[8]	X							
Haematology	X							
Serum Chemistry	X							
Liver Function Testing[9]		X[a]	X			X		
Urinalysis	X							
Urine Pregnancy Test[10]	X	X[a]				X		
Alcohol Breath Test		X[a]						

Table 1 Schedule of Assessments – Overview of Study

Procedure/Assessment	Screening	Injection[a]	1 week post dose	2 weeks post dose	3 weeks post dose	EOT[16]	EOS[17]	TM BUP ET[18]
Visit Number	1	2	3	4	5	6	7	
Day(s)	-30 to -1	1-3	8	15	22	29	43	24-72 hr Post-TM BUP dose
Window (days)			± 1	± 2	± 2	± 2	±5	
UDS[11]	X	X[a]	X	X	X	X		
Self-Reports/TLFB[12]		X[a]	X	X	X	X		
COWS	X	X[a]	X	X	X	X		
OC-VAS	X	X[a]	X	X	X	X		
Sedation VAS		X[a]						
Study Drug Administration		X[a]						
Injection Site Evaluation[13]		X[a]	X	X	X	X		
PK Sampling[14]		X[a]	X	X	X	X		
Counselling[15]		← X →						

AE=adverse event; ALP=alkaline phosphatase; ALT=alkaline aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; BUP=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; ECG=electrocardiogram; EOS=End-of-Study; EOT=End-of-Treatment; ET=Early Termination; GGT=gamma-glutamyl transferase; Hep=Hepatitis; HIV=human immunodeficiency virus; LD=lactase dehydrogenase; LFT=liver function tests; NMP=N-methyl-2-pyrrolidone; OC-VAS=Opioid Craving Visual Analogue Scale; OUD=opioid use disorder; PK=pharmacokinetics; TLFB=TimeLine Follow Back; TM=transmucosal; UDS=urine drug screen; VAS=Visual Analogue Scale

a See Table 2 for detailed schedule of events for Visit 2 (SUBLOCADE Injection)

1. Written informed consent must be obtained before any study-specific assessments/procedures are initiated.
2. Drug use history to include tobacco, alcohol and caffeine use; drugs of abuse (illicit and prescribed). Drugs of abuse and alcohol use will capture the drug class, compounds, and route, dose and frequency of use for lifetime and past 30 days use); and OUD history including MOUD history and prior overdose history.
3. Complete physical examination to include an assessment of general appearance, skin and extremities, head and neck, lymph nodes, eyes, ears, nose, throat, thyroid, neurological system, lungs, cardiovascular system, and abdomen (liver and spleen). The examination will not include a breast, pelvic or rectal exam, unless clinically indicated. Clinically significant abnormal changes from screening will be recorded as AEs.

4. Height will be measured only at the Screening Visit. Body mass index will be calculated within the database using weight and height.
5. Includes systolic and diastolic blood pressure, pulse rate, respiratory rate and oral temperature after the subject has been in a sitting position for ≥3 minutes.
6. An ECG will be collected after the subject has been in a supine position for ≥5 minutes.
7. Includes a review of any previous (taken within 30 days of providing written informed consent) and ongoing medications (including over-the-counter) and herbal supplements.
8. HIV-1/HIV-2, Hep B and Hep C antibody testing to be performed only in the absence of a positive (documented) medical history for these conditions.
9. A sub-set of serum chemistry to be performed including: ALP, ALT, AST, bilirubin, albumin, total protein, GGT and LD only. For increased LFTs, subject should be asked to return to the clinic for weekly repeat liver chemistry testing (ALP, ALT, AST, and total bilirubin) until resolved, stabilised or return to within baseline values, per Section 8.2.7.3.
10. Required for female subjects of childbearing potential only.
11. Qualitative test to be performed for all visits. Additional quantitative test to be performed on Day 1. Additional unscheduled UDS may be performed as necessary.
12. Details subjects illicit drug use, in addition to report question capturing frequency, route and date of last use.
13. Injection site will be evaluated for signs of attempted removal. Any injection site reactions or infections will be recorded as AEs.
14. A 2-mL blood sample will be collected for NMP PK analysis.
15. Subjects will receive counselling during the study as determined by local standard of care.
16. All subjects who receive SUBLOCADE (including those who wish to discontinue early), will be encouraged to attend the EOT visit 28 days after SUBLOCADE administration (Day 29). After enrolment, available treatment options for completed subjects will be discussed.
17. Any subject with ongoing AEs or concomitant medications at the EOT visit and is not continuing MOUD will also be followed up by phone 2 weeks later for the EOS visit (Day 43) to assess the ongoing AEs or concomitant medications only.
18. Subjects who discontinue from the study and have been administered TM buprenorphine but have not been dosed with SUBLOCADE will be followed up via telephone within 24 to 72 hours to assess ongoing AEs and concomitant medications only.

Table 2 Schedule of Assessments – Visit 2: INJECTION

	Day 1														Day 2			Day 3
Procedure/Assessment	**Check-in[1]**	**Pre-TM BUP**	**TM BUP**	**Pre-SUB-LOCADE**	**SUB-LOCADE**	**Post-SUBLOCADE**												
Protocol Time (hours)			**-1**		**0**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**48**
Assessment Window (hours)						**±0.25**				**±1**							**±2**	
PK sampling window (min)				**-10**		**±2**			**±5**	**±15**								
UDS	X																	
Self-Reports/TLFB[2]	X																	
Urine Pregnancy Test[3]	X																	
Alcohol Breath Test[4]	X																	
COWS & OC-VAS[5]	X	X		X		X	X	X	X	X	X	X	X[6]	X[6]	X	X	X	X
Concomitant Medications[7]	←							X										→
AE Assessment	←							X										→
Sedation VAS		X		X		X			X		X	X	X[6]	X[6]	X	X	X	X
Vital Signs[8]		X		X		X			X		X	X			X	X	X	X
12-Lead ECG[9]		X													X			X
TM BUP administration			X[10]															
Liver Function Testing[11]			X[13]															
Weight[12]			X[13]															
SUBLOCADE administration					X[14]													
Injection Site evaluation[15]						X			X			X			X		X	X
PK Sampling[16]				X		X	X		X	X	X	X			X	X	X	X
Counselling[17]		←						X										→
Check Out of Clinic[18]																		X

AE=adverse event; ALP=alkaline phosphatase; ALT=alkaline aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; BUP=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; ECG=electrocardiogram; GGT=gamma-glutamyl transferase; PK=pharmacokinetics; OC-VAS=Opioid Craving Visual Analogue Scale; LD=lactase dehydrogenase; LFT=liver function test; TLFB=TimeLine Follow Back; TM=transmucosal; UDS=urine drug screen; VAS=Visual Analogue Scale

1. Upon arriving at the clinic, subjects will provide a urine sample for a UDS for qualitative and quantitative analysis, a urine sample for a pregnancy test (child-bearing females only), perform an alcohol breathalyser test and self-report their concomitant medications since screening and recent illicit drug use (including the use of a TimeLine Follow Back [TLFB]). If subject is deemed eligible for check-in the subject will then be assessed for withdrawal symptoms using COWS and for craving using OC-VAS.
2. Details subjects illicit drug use, in addition to report question capturing frequency, route and date of last use.
3. Required for female subjects of childbearing potential only.
4. Per Investigator's discretion, subjects with positive test may either remain in the clinic or be re-scheduled to return on another date.
5. Per Investigator's discretion, subjects with COWS <8 may either remain in the clinic and repeat assessments at a later time or be re-scheduled to return on another date. The COWS may be repeated at any time, per Investigator's discretion, and should always be repeated just before TM-BUP and SUBLOCADE administration. The OC-VAS should be performed each time a COWS assessment is performed.
6. If the subject is asleep at 16 and 20 hours, the assessments will not be performed, and the reason should be noted in the CRF.
7. Includes a review of any previous (taken since screening) and ongoing medications (including over-the-counter) and herbal supplements.
8. Includes systolic and diastolic blood pressure, pulse rate, respiratory rate and oral temperature after the subject has been in a sitting position for ≥3 minutes.
9. An ECG will be collected after the subject has been in a supine position for ≥5 minutes.
10. Eligible subjects must meet the buprenorphine dosing criterion, prior to receiving 4mg TM buprenorphine.
11. A sub-set of serum chemistry to be performed including: ALP, ALT, AST, bilirubin, albumin, total protein, GGT and LD only. For increased LFTs, subject should be asked to return to the clinic for weekly repeat liver chemistry testing (ALP, ALT, AST, and total bilirubin) until resolved, stabilised or return to within baseline values, per Section 8.2.7.3.
12. Weight to be captured; BMI will be calculated in the database using height from screening.
13. Assessment to be performed anytime pre-SUBLOCADE dose.
14. Eligible subjects meet SUBLOCADE dosing criteria, prior to receiving SUBLOCADE.
15. Injection site will be evaluated for signs of attempted removal. Any injection site reactions or infections will be recorded as AEs.
16. A 2-mL blood sample will be collected for NMP PK analysis at each time point. The PK samples should be collected as closely as possible to the nominal times, permitted windows are present in the header in minutes. The pre-dose PK sample should be performed after the subject has been confirmed eligible for SUBLOCADE dosing.
17. Subjects will receive counselling during the visit as determined by local standard of care.
18. Subjects will check out of clinic upon completion of all scheduled assessments.

5 POPULATION

5.1 Number of Subjects

Approximately 15 adult subjects with moderate or severe OUD are planned to be dosed with SUBLOCADE.

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 the time of signing the ICF.

3. Have documented history of moderate or severe OUD as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).

4. Seeking buprenorphine-assisted treatment for OUD and is an appropriate candidate in the opinion of the Investigator or medically qualified sub-Investigator.

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

5.3 Exclusion Criteria

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

2. Meet DSM-5 criteria for severe alcohol-use disorder.

3. Has received any medication assisted treatment within 2 weeks.

4. Concurrent or prior treatment with any long-acting depot form of buprenorphine-containing products.

5. Concurrent treatment with another investigational agent or enrolment in another clinical study (except for an observational study) or treatment with another investigational agent within 30 days prior to screening.

6. Concurrent treatment with medications contraindicated for use with buprenorphine as per local prescribing information, including benzodiazepines or any other central nervous system depressants.

7. Significant traumatic injury, major surgical procedure (as defined by the Investigator) within 30 days prior to Day 1 or still recovering from prior surgery.

8. Any other active medical condition, organ disease or concurrent medication or treatment that may either compromise subject safety or interfere with study endpoints.

9. Congenital long QT syndrome, history of prolonged QT in the 3 months prior to screening, or a corrected QT interval (Fridericia's – QTcF) >450 msec (male) or >470 msec (female), or history of risk factors for Torsades de Pointes. Known personal and/or family history of congenital QT prolongation, or taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone) or other mediations that prolong the QT interval. Known family history of sudden unexplained death.

10. Total bilirubin ≥1.5 × ULN, ALT ≥3 × ULN, AST ≥5 × ULN, serum creatinine >2 × ULN at screening.

11. Abdominal area unsuitable for SC injections (e.g., nodules, lesions, excessive pigment, infected, scarring).

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

13. Known allergy or hypersensitivity to buprenorphine, ATRIGEL or their excipients.

14. Subject to court order requiring treatment for OUD.

15. Subjects who are unable, in the opinion of the Investigator or Indivior, to comply fully with the study requirements including those who are currently incarcerated or pending incarceration/legal action.

16. Clinic staff and/or subjects who have a financial interest in the study or who have an immediate family member of either the clinic staff and/or Indivior employees directly involved in the study.

5.4 Subject Screening

Subjects who provide written informed consent will enter a Screening Period to confirm study eligibility.

Eligible subjects will be advised to abstain from short-acting opioids (such as morphine sulfate, oxycodone, hydromorphone, oxymorphone or codeine) for at least 6 hours and long-acting opioids (such as methadone or levorphanol) for 24 hours before arriving at the clinic on the morning of Day 1. Eligible subjects will be informed that under-reporting of the last use of opioids puts him/her at higher risk for rapid and intense onset of withdrawal symptoms. Eligible subjects will also be advised to abstain from alcohol before checking into the clinic.

5.5 Day 1 Check-in Criteria

Subjects must meet all of the following criteria to check into the clinic:

1. All childbearing female subjects must have a negative urine pregnancy test.

2. Subject self-reports/TLFB that they have not had any long-acting opioids within 24 hours.

3. Blood alcohol concentration (per breathalyser) is not of concern to the Investigator.

4. Subject is not taking any medications (illicit or prescribed) contraindicated for use with buprenorphine as per local prescribing information, including benzodiazepines or any other central nervous system (CNS) depressants.

Subjects who indicate that they have used long-acting opioids within 24 hours, or who have a blood alcohol concentration (per breathalyser) of concern to the Investigator, will not be permitted to check in and may be re-scheduled for check-in within the Screening Period. Subjects who report having used short-acting opioids within 6 hours may be permitted to check in at the discretion of the Investigator.

5.6 Buprenorphine Dosing Criterion

Subjects must be in withdrawal (COWS ≥8) to receive 4-mg TM buprenorphine.

If a subject's COWS is not ≥8, the subject may either be re-scheduled for check-in within the Screening Period or remain in the clinic (at the Investigator's discretion), and the COWS may be repeated until the subject achieves a score ≥8. Only when the COWS is ≥8 and all pre-buprenorphine assessments have been completed may the subject receive TM buprenorphine.

5.7 SUBLOCADE Dosing Criteria

One hour after TM buprenorphine, the subject will complete pre-dose/SUBLOCADE assessments including COWS, OC-VAS, Sedation VAS, AEs, vital signs and concomitant medications.

Subjects must meet all of the following criteria to receive SUBLOCADE:

1. Subject does not display any allergic/hypersensitivity reaction to buprenorphine.
2. Precipitated withdrawal did not occur from the most recent TM buprenorphine administration.
3. Subject does not display clinical signs of sedation, in the opinion of the Investigator.

5.8 Deviation from Inclusion/Exclusion Criteria

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

6 STUDY CONDUCT

6.1 Subject Screening

Study screening begins once written informed consent is obtained; a subject identification number is then assigned. The subject identification number 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 do not meet study eligibility criteria (i.e., screen failures), including reason(s) for ineligibility (i.e., a subject screening and enrolment log). This document will be reviewed by Indivior or designated representative for accuracy and completeness. Ineligible subjects, as defined by the protocol-specific inclusion and exclusion criteria, should not receive study drug and should be documented as screen failures.

6.2 Screen Failure

A subject will be considered a screen failure if written informed consent is obtained but the subject does not receive TM buprenorphine. Subjects who discontinue from the study before TM buprenorphine administration will not be required to complete an ET or EOT visit. Reasons for screen failure (e.g., withdrawal of consent, does/not meet specified inclusion or exclusion criteria, or does not meet specific Day 1 check-in criteria) will be recorded in the electronic case report form (eCRF).

6.3 Enrolment

A subject will be considered enrolled if he/she receives at least 1 dose of TM buprenorphine.

6.4 TM Buprenorphine Treatment and Early Termination

When an eligible subject's COWS is ≥8 and all pre-buprenorphine assessments have been completed, the subject will receive TM buprenorphine. Subjects experiencing precipitated withdrawal will be treated for withdrawal symptoms. If precipitated withdrawal occurs before SUBLOCADE administration, the TM induction may be restarted later on the same day at the discretion of the Investigator, based on the half-life of the opioid reported on the TLFB. Alternatively, the Investigator may permit the subject to return to the facility on another day (within the Screening Period). Returning subjects will repeat all Day 1 scheduled assessments.

A subject will be considered a TM Buprenorphine Early Termination if he/she is dosed with TM buprenorphine but is not dosed with SUBLOCADE. Reasons for early termination (e.g., withdrawal of consent, AE of precipitated withdrawal, allergic/hypersensitivity to buprenorphine) will be recorded in the eCRF. Subjects who discontinue from the study after TM buprenorphine administration and before SUBLOCADE administration, will be withdrawn from the study and contacted via

telephone 24 to 72 hours after TM buprenorphine administration to assess ongoing AEs and concomitant medications only.

6.5 SUBLOCADE Treatment

SUBLOCADE treatment begins when the SUBLOCADE injection is given and ends on Day 29 after all assessments have been made at Visit 6.

6.6 Subject Completion

A completed subject is one that has completed all scheduled visits up to and including the EOT Visit (Day 29).

6.7 Withdrawal and Stopping Criteria

6.7.1 Subject Withdrawal from the Study

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

Subjects who discontinue from the study before TM buprenorphine administration will be considered a screen failure and will not be required to complete an ET or EOT visit.

Subjects who discontinue from the study after TM buprenorphine administration, and before SUBLOCADE administration will not be required to complete an EOT visit but will be contacted via telephone 24 to 72 hours after TM buprenorphine administration to assess AEs and concomitant medications only.

All subjects who receive SUBLOCADE (including those who wish to discontinue early), will be encouraged to attend the EOT visit 28 days after SUBLOCADE administration (Day 29), as well as the EOS visit via telephone (Day 43).

6.7.2 Subject Withdrawal of Consent

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

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

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

- In the case where a certified letter is sent but not confirmed as received by the subject, the date of discontinuation is the date the certified letter was sent.

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

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

7 STUDY SUSPENSION OR TERMINATION

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

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

8 DESCRIPTION OF STUDY PROCEDURES

Study assessments and procedures, including the timing of assessments, are summarised in Table 1 and Table 2. Further details on safety assessments are provided in Section 8.2.

A signed written ICF must be obtained from the subject or a legal representative 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/Psychiatric/Drug use History

A detailed medical and psychiatric history will be obtained during the Screening Period. This will include information regarding the subject's complete history of relevant

medical and psychiatric conditions, diagnoses, procedures, treatments, medications, demographics (including sex, race, age and ethnicity), tobacco, alcohol, caffeine and drug of abuse. Drugs of abuse (illicit and prescribed) and alcohol use will capture the drug class, compounds, and route, dose and frequency of use for lifetime and past 30 days use.

Eligible subjects must have a documented diagnosis of OUD prior to screening as defined by DSM-5 and must be seeking MOUD. Any updates to medical or psychiatric history information made available during the study will be captured. Demographics and medical and psychiatric history will be recorded in the source documents and the eCRF per the Schedule of Events in Table 1.

An alcohol breath test will be administered at check-in on Day 1 (Table 2).

8.2 Safety Assessments

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

8.2.1 Urine Drug Screening (UDS)

A qualitative UDS will be conducted as per the schedules of events in Table 1 and Table 2. A quantitative UDS also will be performed on Day 1 only. The UDS will include substances listed in Table 3.

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

8.2.2 Opioid Craving Visual Analogue Scale (VAS)

A VAS is an instrument that measures a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. The amount of opioid craving that a subject feels for illicit opioids (not the buprenorphine used for treatment of OUD) can be recorded along a continuum from "no craving at all" to "strongest craving ever" (McMillan 1996). The level 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".

For this study, the Opioid Craving VAS (OC-VAS) is a horizontal line, using a 100-millimetre (mm) scale anchored by word descriptors at each end of "no craving" (0 mm) to "strongest craving ever" (100 mm). The subject marks the point on the line that he/she feels represents his/her perception of their current state at the time. The VAS score is calculated as the difference from the left-hand end of the line to the point that the subject marked.

The OC-VAS will be assessed as per the schedule of assessments in Table 1 and Table 2.

The OC-VAS will be recorded on paper source by the subject and will then be entered into the subject's eCRF by the site.

8.2.3 Clinical Opiate Withdrawal Scale (COWS)

The COWS is an 11-item, validated instrument used to assess symptoms of opiate withdrawal (Tompkins 2009, Wesson 2003). The score is the sum of the response to each of the 11 items and ranges from 0 to 48. A score of 5 to 12 is considered mild, 13 to 24 is moderate, 25 to 36 is moderately severe, and a score >36 is considered severe withdrawal. Where feasible, each subject should be assessed by the same qualified and trained individual throughout the course of the study.

The COWS will be assessed as per the schedule of assessments as shown in Table 1 and Table 2.

8.2.4 TimeLine Follow Back (TLFB) and Self-reports

The TLFB Interview is a method to assess recent drug use administered by an interviewer. The subject is asked to retrospectively estimate their drug use in the 30 days prior to screen at the Screening Visit and since the last visit at all subsequent visits. Only "used" or "did not use" is captured in the TLFB (Fals-Stewart 2000), therefore an additional self-report question capturing frequency, route of last use and date of last use will also be added to those answered "used". The interview takes approximately 10 to 30 minutes to complete and is appropriate for males and females 14 years of age and older. Drugs to be assessed in this study include opioids (including fentanyl, oxycodone, methadone, and buprenorphine), cocaine, barbiturates, benzodiazepines, amphetamines/methamphetamine, phencyclidine, cannabinoids and ethanol.

A TLFB/self-report interview will be conducted as per the schedule of assessments in Table 1 and Table 2.

The TLFB/self-report interview responses will be recorded on paper source by the clinic and will then be entered into the subject's eCRF.

8.2.5 Physical Examination

A complete physical examination will be conducted by the Investigator or a medically qualified sub-Investigator at screening and EOT (Table 1). This examination will include an assessment of general appearance, skin and extremities, head and neck, lymph nodes, eyes, ears, nose, throat, thyroid, neurological system, lungs, cardiovascular system, and abdomen (liver and spleen). The examination will not include a breast, pelvic or rectal exam, unless clinically indicated.

If any clinically significant change from screening is noted, it will be reported as an AE and followed to resolution or until reaching a stable endpoint. Details of the physical examination will be recorded in the source document.

Weight (kg) will be assessed as per the schedule of assessments in Table 1 and Table 2. Height (cm) will be recorded at screening only.

The SUBLOCADE injection site will be evaluated for signs of attempted depot removal. Any removals will be reported as an AE of special interest as directed in Section 10.1. Any injection site reactions or infections will be recorded as AEs. Injection site evaluations will be performed according to the schedule of assessments, as shown in Table 1 and Table 2.

8.2.6 Sedation VAS

For this study, the Sedation VAS is a horizontal line, using a 100-millimetre (mm) scale anchored by word descriptors at each end: "Not at all" (0 mm) to "Almost asleep" (100 mm). The subject will mark the point on the line that he/she feels represents his/her perception of the current state of sedation at the time. The VAS score is calculated as the difference from the left-hand end of the line to the point that the subject marked.

The subject will complete a VAS question for sedation as per the schedule of assessments in Table 1 and Table 2.

The Sedation VAS responses will be recorded on paper source by the subjects and will then be entered into the subject's eCRF by the site.

8.2.7 Clinical Laboratory Tests

Clinical laboratory tests will be performed in a licensed clinical laboratory. Urine pregnancy tests may be performed using a licensed test (dipstick). Subjects are to be in a sitting/supine position during blood collection.

The following clinical laboratory tests (Table 3) will be performed according to the schedule of assessments, as shown in Table 1 and Table 2.

Table 3 List of Laboratory Tests

Screening Only	**Serum Chemistry:**	**Pregnancy:**
Haematology:	Albumin	Urine pregnancy (if applicable)
Haematocrit	Alkaline phosphatase (ALP)	
Haemoglobin	Alanine aminotransferase (ALT)	**Urine Drug Screen (UDS):**
Mean corpuscular haemoglobin	Amylase	Opioids
Mean corpuscular haemoglobin concentration	Aspartate aminotransferase (AST)	Cocaine
Mean corpuscular volume	Blood urea nitrogen	Amphetamines
Platelet count	Calcium	Methadone
Red blood cell (RBC) count	Calculated creatinine clearance	Cannabinoids
White Blood Cell (WBC) count with 5-part differential	Carbon dioxide	Barbiturates
	Chloride	Benzodiazepines
Urinalysis:	Creatinine	Methamphetamine
Appearance	Creatine kinase and subtypes	Phencyclidine
Bilirubin	Gamma-glutamyl transferase (GGT)	Fentanyl
Colour	Globulin	Oxycodone
Glucose	Glucose (non-fasting)	Morphine
Ketones	Lactate dehydrogenase (LD)	
Leucocyte esterase	Lipase	
Microscopic examination of sediment[1]	Magnesium	
Nitrite	Phosphorus	
Occult blood	Potassium	
pH	Sodium	
Protein	Total bilirubin	
Specific gravity	Direct bilirubin	
Urobilinogen	Total cholesterol	
	Total protein	
Other:[2]	Triglycerides	
HIV-1 and -2 antibodies	Uric acid	
Hep C and Hep B antibodies		

Hep=hepatitis; HIV=human immunodeficiency virus; WBC=white blood cell

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

[2] To be performed only in the absence of a positive (documented) medical history for these conditions.

8.2.7.1 Sample Collection, Storage and Shipping

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

8.2.7.2 Laboratory Result Review

The Investigator or a medically qualified sub-Investigator will review the laboratory results and clearly identify those that are "abnormal, not clinically significant (NCS)" as well as those that are "abnormal, clinically significant". Any abnormal clinically

significant laboratory value will be reported as an AE in the eCRF. The Investigator or a medically qualified sub-Investigator will sign and date laboratory reports as evidence of review.

8.2.7.3 Liver Chemistry Review Criteria

The Liver Chemistry Review Criteria for post-dose values are as follows:

1. The subject has ALT >3 × ULN **and** bilirubin >2 × ULN (>35% direct bilirubin).
2. The subject has ALT >3 × ULN and 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).
3. The subject has ALT >5 × ULN but <8 × ULN persisting for >2 weeks.
4. The subject has ALT >5 × ULN but <8 × ULN and cannot be monitored weekly for ≥2 weeks.
5. The subject has ALT >8 × ULN.

If the subject experiences Criterion 1, this is an SAE (important medical event) of special interest, that must be reported to Indivior as per Section 11.2.1. The subject should be asked to return to the clinic within 24 hours for repeat liver chemistries, additional testing and close monitoring (with specialist or hepatology consultation recommended).

If any subject meets any of Criteria 2 through 5, the Indivior medical monitor should be notified, and the subject should be asked to return to the clinic for weekly repeat liver chemistry testing (ALP, ALT, AST, and total bilirubin) until resolved, stabilised or return to within baseline values.

If clinically indicated, the SUBLOCADE depot may be surgically removed within 14 days of injection. See Section 10.7 for details on reporting depot removal.

8.2.8 Pharmacokinetic Sampling

Blood samples (2 mL each) will be collected from subjects according to the schedule of assessments, as shown in Table 1 and Table 2, for the determination of NMP plasma concentration. The exact times (to the minute) of PK blood sampling will be recorded in data source. The pre-dose PK sample should be taken only after the subject is deemed eligible to receive SUBLOCADE dosing.

Permitted blood sampling windows for the Injection visit are as follows:

Timepoint (Hours)	**Pre-dose**	**1**	**2**	**4**	**6**	**8**	**12**	**24**	**30**	**36**	**48**
Window (minutes)	**-10**	**±2**		**±5**	**±15**						

Blood samples collected during the post-injection visits will be permitted to be drawn within the visit windows only:

	1-week post dose	2 weeks post dose	3 weeks post dose	EOT
Visit Number	3	4	5	6
Window (Days)	±1	±2	±2	±2

Plasma concentrations of NMP will be quantified using a specific and validated liquid chromatography tandem mass spectroscopy method. A laboratory manual for PK sample collection, processing, storage and shipping will be supplied.

8.2.9 Vital Signs

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

Vital signs will be performed according to the schedule of assessments, as shown in Table 1 and Table 2.

8.2.10 12-Lead Electrocardiograms

Electrocardiograms should be collected on the same model ECG machine, where feasible. All ECGs will be performed after the subject has been in a supine position for ≥5 minutes. Recordings will be taken using an ECG machine that automatically calculates the heart rate and measures QT, QTc (Fridericia's) intervals and can perform an arrhythmia analysis.

The findings of the ECGs will be marked by the Investigator or medically qualified sub-Investigator as normal; abnormal - NCS; or abnormal - clinically significant. All ECGs that are considered abnormal and clinically significant should be evaluated for a change from baseline and must be captured as an AE.

12-Lead ECGs will be performed according to the schedule of assessments, as shown in Table 1 and Table 2.

8.3 Protocol Deviations

A protocol deviation is any non-compliance with the clinical study protocol or ICH/GCP requirements. The non-compliance may be on the part of the subject, the Investigator or the study clinic staff. As a result of deviations, corrective actions are to be developed by the clinic and implemented promptly and in accordance with ICH E6. It is the responsibility of the Investigator and study clinic staff to use continuous vigilance to identify and report deviations to Indivior or specified designee and the IRB. All

deviations must be reported in the study source documents. Protocol deviations must be sent to the IRB as required. The Investigator and study clinic staff are responsible for knowing and adhering to the IRB's requirements.

9 STUDY DRUG MANAGEMENT

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

The clinic will source commercially available TM buprenorphine for the study; SUBLOCADE will be provided by the Sponsor.

9.1 Description

9.1.1 Formulation

SUBLOCADE 300 mg is a colourless to amber sterile solution for SC injection designed to deliver buprenorphine at a dose of 300 mg at a controlled rate over a 1-month period. The active ingredient in SUBLOCADE 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.

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

9.1.2 Storage

SUBLOCADE must be stored in a refrigerator at 2° to 8°C (35.6° to 46.4°F) in accordance with the USPI, in a secure location with limited access. Once outside the refrigerator, SUBLOCADE may be stored in its unopened original packaging at room temperature, 15°C to 30°C (59°F to 86°F), for up to 7 days prior to administration. Discard SUBLOCADE if left at room temperature for longer than 7 days.

The TM buprenorphine should be stored according to instructions in the USPI.

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

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

9.2 Packaging and Labelling

The SUBLOCADE clinical study labels will be developed in accordance with Good Manufacturing Practice (GMP) and local regulatory requirements. Detailed information regarding the commercial packaging of SUBLOCADE is outlined in the USPI.

SUBLOCADE inner packaging (pouch) must remain with the outer product carton until the time of administration.

9.3 Shipment

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

9.4 Dose and Administration

Eligible subjects will be advised to abstain from short-acting opioids (such as morphine sulfate, oxycodone, hydromorphone, oxymorphone or codeine) for at least 6 hours and long-acting opioids (such as methadone or levorphanol) for 24 hours before arriving at the clinic on the morning of Day 1. Eligible subjects will be informed that under-reporting of the last use of opioids puts him/her at higher risk for rapid and intense onset of withdrawal symptoms.

9.4.1 Transmucosal Buprenorphine

Subjects are required to be in withdrawal (COWS ≥8) prior to administration of TM buprenorphine 4 mg. The TM buprenorphine will be administered as per the instructions for use in the USPI. The dose will be given in the clinic followed by a 1-hour wait.

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

9.4.2 SUBLOCADE Extended-release Injection

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

Eligible subjects must not display any of the following on assessment after TM buprenorphine: any allergic/hypersensitivity reaction to TM buprenorphine, evidence of precipitated withdrawal, or clinically significant sedation, in the opinion of the Investigator.

SUBLOCADE should be administered as per the instructions for use in the SUBLOCADE USPI Section 2.6.

Time of dose for SUBLOCADE is defined as the time the SC injection is complete. The time of dose and any dosing observations (e.g., partial doses or other issues with the

injection) will be recorded in the source documentation; in addition, time of dose will be recorded in the eCRF.

The Investigator will not supply SUBLOCADE to any person except study personnel for SC injection of subjects in this study.

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

9.5 Accountability

The Investigator is responsible for ensuring that all study drug received at the clinic is inventoried, accounted for and documented in accurate accountability records. Accountability records will be provided to Indivior. All unused study drug will be destroyed by the Investigator, as per local standard operating procedures (SOP). The study drug must be handled strictly in accordance with the protocol, handling guidelines and the USPI; it must be stored in a locked, limited-access area under appropriate environmental conditions.

The dispensing of study drug to the subject must be documented on the drug dispensing form. All study drug dispensation will be performed by a pharmacist or designee, checked by a study centre staff member and documented on a drug dispensation form.

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

9.6 Concomitant Therapies

Concomitant medications will be collected from screening until the EOT at the time points listed in Table 1 and Table 2. Any subject with ongoing concomitant medications at the EOT and not continuing MOUD will also be followed up by phone 2 weeks later for the EOS visit (Day 43) to assess the ongoing concomitant medications. 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.

9.7 Prohibited Concomitant Therapies

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

Supplemental TM buprenorphine (after SUBLOCADE injection) may only be permitted after discussions with the medical monitor.

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 USPI should be referenced regarding use of the below concomitant therapies.

- benzodiazepines and other CNS depressants
- cytochrome P450 3A4 inhibitors or inducers (see Appendix 1)
- antiretrovirals: non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- antiretrovirals: protease inhibitors
- serotonergic drugs
- monoamine oxidase inhibitors (MAOIs)
- muscle relaxants
- diuretics
- anticholinergic drugs

The Indivior medical monitor should be notified if a subject receives any of these treatments during the study.

9.8 Lifestyle Restrictions

Eligible subjects will be advised to abstain from short-acting opioids (such as morphine sulfate, oxycodone, hydromorphone, oxymorphone or codeine) for at least 6 hours and long-acting opioids (such as methadone or levorphanol) for 24 hours before arriving at the clinic on the morning of Day 1. Eligible subjects will be informed that under-reporting of the last use of opioids puts him/her at higher risk for rapid and intense onset of withdrawal symptoms.

Eligible subjects will be advised to abstain from alcohol before checking into the clinic for Day 1 procedures and throughout the study, as central nervous system depressants increase the risk of respiratory depression, profound sedation, coma and death in patients taking buprenorphine (SUBLOCADE USPI).

9.9 Permitted Concomitant Therapies

The Investigator may prescribe concomitant medications or treatments deemed necessary to the subject, except those medications defined in Section 9.7 of this protocol.

Subjects experiencing precipitated withdrawal will be treated for withdrawal symptoms. If precipitated withdrawal occurs before SUBLOCADE administration, the TM induction may be restarted later on the same day at the discretion of the Investigator, based on the half-life of the opioid reported on the TLFB. Alternatively, the Investigator may permit

the subject to return to the facility on another day (within the Screening Period). Returning subjects will repeat all Day 1 scheduled assessments.

If the subject experiences withdrawal symptoms at any time (including precipitated withdrawal after SUBLOCADE), he/she may be treated symptomatically (SAMHSA TIP 63 2018):

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

Supplemental TM buprenorphine (after SUBLOCADE administration) may only be permitted after discussions with the medical monitor. Subjects will not be discontinued from treatment due to illicit opioid use (including buprenorphine).

9.10 Compliance

All study drugs will be administered in the clinic and documented in the source and recorded in the eCRF.

SUBLOCADE compliance will be assessed by inspecting the injection site for evidence of attempted removal of the depot by the subject, 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. See Section 10.7 for details on reporting depot removal.

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

9.11 Reporting Product Complaints

The Investigator and study clinic 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 study drug and includes, but is not limited to, e.g., short counts/empty pouches, leaking syringes, broken needles, labelling defects, missing inserts, packaging defects or difficult to open packaging, study drug that is thought to be ineffective, or has an appearance, taste or odour that is outside of what is expected.

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

- study number
- site contact/reported by
- 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.

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

Events meeting the definition of an AE include:

- New condition detected after study drug administration even though the AE may have been present prior to receiving study drug.
- Exacerbation of a pre-existing condition (including intensification of a condition and/or an increase in frequency).
- Any abnormal laboratory test results or other safety assessments felt to be clinically significant in the opinion of the Investigator (including those that worsen from baseline).
- Symptoms and/or the clinical sequelae of a suspected interaction or an overdose of either study drug or a concomitant medication
- Signs, symptoms or the clinical sequelae resulting from special interest conditions (e.g., medication error, SUBLOCADE depot removal, etc.).
- 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.
- Evidence of a subject attempting removal of the SUBLOCADE depot

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

- Medical or surgical procedures; the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, hospitalisation for elective surgery, hospitalisation for observation in the absence of an AE).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.1 AEs of Special Interest

In this study, AEs of special interest include the following:

- SUBLOCADE depot removal (see Section 10.7)
- Occurrences of ALT ≥3 × ULN and bilirubin ≥2 × ULN (> 35% direct) are defined as SAEs of special interest

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

10.2 Assessing and Documenting Adverse Events

The Investigator is ultimately responsible for assessing and reporting all AEs as outlined in the protocol. The assessment and reporting of AEs may be delegated to a medically qualified sub-Investigator, trained on this study protocol, who is listed on the delegation of authority log. All AEs regardless of suspected causal relationship to the study drug 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 clinic visit, or from observations of clinically significant laboratory values or special examination abnormal values. If an event assessed by one of the study scales requires intervention, or if in the opinion of the Investigator, it is clinically significant, then it will be reported as an AE.

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

10.3 Time Period for Collecting Adverse Events

Adverse events will be collected from the time of signed informed consent until completion of the EOT visit. Any subject with ongoing AEs at the EOT and not continuing MOUD will also be followed up by phone 2 weeks later for the EOS visit (Day 43) to assess the ongoing AEs.

Subjects with ongoing SAEs at the EOS telephone contact that, in the opinion of the Investigator, are associated with the study drug, will be followed and reported as described in Section 11. Subjects with ongoing AEs at EOS telephone contact that, in the opinion of the Investigator, are associated with the study drug, will be followed and reported as described in Section 10.2.

10.4 Assessment of Intensity

The term "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on 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; hospitalisation is probable

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

10.5 Assessment of Causality

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

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

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

Related: The cause of the AE is related to the study drug and cannot be reasonably explained by other factors (e.g., the 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 that a relationship cannot be ruled out. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the study drug will be considered and investigated. The Investigator will also consult the USPI in the determination of his/her assessment. For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

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

10.6 Clinical Laboratory Changes

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

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

Guidance for the procedures to follow for elevated liver function tests are provided in Section 8.2.7.3.

10.7 SUBLOCADE Depot Removal

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

11 SERIOUS ADVERSE EVENT

11.1 Definition of Serious Adverse Event

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

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

- Death
- Life-threatening
- Inpatient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Other: Important medical events that may not result in death, be life-threatening or require hospitalisation, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the 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 hospitalisation
- Subjects with ALT ≥3 × ULN and bilirubin ≥2 × ULN (> 35% direct) are defined as SAEs of special interest (important medical event), and should be reported to Indivior by the Investigator (or designee) **within 24 hours** from first being aware of the event, using the same reporting process as for SAEs, See Section 11.2. Potential Hy's Law cases should be managed as described in Section 8.2.7.3.

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, study drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though study drug-induced hepatitis can be fatal.

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

In general, hospitalisation signifies that the 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 hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

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

11.2 Documenting Serious Adverse Events

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

It is not acceptable for the Investigator to send photocopies of the 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.

11.2.1 Investigator Reporting of Serious Adverse Events

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

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

In the event of an SAE, the Investigator or designee will notify Indivior Global Safety by completing the paper SAE Reporting Form and submitting the form to Indivior Global Safety via email or fax:

Email: [redacted]
Fax: [redacted]

11.2.2 Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

12 PREGNANCY

12.1 Collecting and Reporting Pregnancy Information

Information on all pregnancies will be collected from receipt of study drug until 3 months following the last dose of TM buprenorphine and until 12 months following the last dose of SUBLOCADE (approximately 5 terminal half-lives). All confirmed pregnancies that occur within this study will be followed until resolution (i.e., termination [voluntary or spontaneous] or birth).

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

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

Any pregnancy complication or elective termination for medical reasons must be reported as an AE or SAE. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the 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 representative. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a pregnancy 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) after SUBLOCADE administration and before EOT, the subject will undergo a urine pregnancy test at the next scheduled visit.

If a urine pregnancy test confirms that the subject is pregnant, she will undergo all remaining study visit procedures (with the exception of any additional pregnancy testing), as no further study drug will be administered. The Investigator should fully inform the female subject of the potential risk to the foetus.

Removal of the SUBLOCADE depot will not be required if pregnancy occurs.

13 DATA MANAGEMENT

13.1 Data Collection and Management

Data will be entered into the eCRF and will be combined with other data captured centrally outside of the eCRF into a validated system. Clinical data will be managed in accordance with the data management plan to ensure that the integrity of the data is maintained. Adverse events, medical history and indication for concomitant medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The eCRFs (including queries and audit trails) will be retained by Indivior. An electronic copy of the eCRF will be sent to the Investigator to maintain for their records. Subject identifiers will not be collected or transmitted to Indivior according to Indivior standards and procedures. Data collection will be completed according to the study plans.

13.2 Database Quality Assurance

The eCRFs will be reviewed and checked for omissions, apparent errors and values requiring further clarification using 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 in an audit trail.

13.3 Source Documentation

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

Study data are not to be gathered directly onto the eCRF but must be gathered onto primary source documents at the site. Completion of source documents will precede the completion of the eCRF. Source documents may be electronic, hard copy, or a combination of both and are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the Investigator and made available for direct inspection by the authorized study personnel.

14 STATISTICS

14.1 General Procedures

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

All safety data will be listed.

Continuous variables will be summarised using descriptive statistics such as mean, standard deviations (SD), median, minimum and maximum. Categorical variables will be reported as frequency counts (including number missing) and the percentage of subjects in corresponding categories. Individual subject data will be presented by subject in data listings. Data listings will include all data collected from the initial screening visit to the EOS for all subjects enrolled. A statistical analysis plan (SAP) will be prepared after the protocol is approved and before database lock occurs. The SAP will provide further details regarding analysis. Additional unplanned analyses may be required after all planned analyses have been completed. Any deviations from the analyses described below will be outlined in the SAP. Any unplanned analyses will be clearly identified in the clinical study report.

14.2 Sample Size

Approximately 15 adult subjects with moderate to severe OUD are planned to be dosed with SUBLOCADE. If a subject prematurely discontinues from the study, additional subjects may be enrolled to ensure that 15 subjects are dosed with SUBLOCADE and are evaluable for precipitated withdrawal (see Section 14.3.1).

With a sample size of 15, the probability to observe at least one case of precipitated withdrawal is 79.4%, assuming the true event rate is 10%, while the probability to observe at least one case of precipitated withdrawal is reduced to 53.7% if the true event rate is 5%. Table 4 provides the probabilities of observed events at different true event rates.

Table 4 Probabilities of Observed Events at Different True Event Rates

True Event Rate	0 event	At Least 1 Event	At Least 2 Events	At Least 3 Events
1%	0.860	0.140	0.010	0.0004
5%	0.463	0.537	0.171	0.036
8%	0.286	0.714	0.340	0.113
10%	0.206	0.794	0.451	0.184
15%	0.087	0.913	0.681	0.396
20%	0.035	0.965	0.832	0.602

14.3 Analysis Populations

14.3.1 Full Analysis Set (FAS)

The FAS population consists of all subjects who receive a SUBLOCADE injection and are evaluable for precipitated withdrawal; i.e., having data for at least 1 COWS assessment before SUBLOCADE injection and COWS assessments for 48 hours after SUBLOCADE injection. The FAS will serve as the primary population for the analysis of key endpoints in this study.

14.3.2 Safety Analysis Set

The safety population will be used for the safety analysis, and it consists all subjects who received at least 1 dose of SUBLOCADE. The safety population will serve as the primary population for the analysis of other safety assessments.

14.3.3 TM Buprenorphine Analysis Set

The TM Buprenorphine Analysis Set consists of all subjects who received at least 1 dose of TM buprenorphine. This analysis set will be used for analysis of the exploratory safety endpoint.

14.3.4 PK Analysis Set

The PK Analysis Set will be used for the Exploratory PK endpoint analysis and will consist of all subjects who receive the SUBLOCADE injection and are evaluable for PK, i.e., having an adequate number of PK samples collected to derive PK parameters. Subjects in the PK population with protocol deviations or events that impact the quality of the PK data will be assessed on a case-by-case basis.

14.4 Analysis of Key and Exploratory Endpoints

14.4.1 Key Endpoints

The number and percentage of subjects who experience precipitated withdrawal (defined as an increase in COWS by ≥6 from the pre-SUBLOCADE value) within approximately 1 hour after SUBLOCADE administration will be summarized. The frequency count, percentage and its 2-sided 95% exact confidence interval (CI) using binomial distribution (Clopper-Pearson method) will be constructed for precipitated withdrawal from the pre-SUBLOCADE value, using the FAS.

The number and percentage of subjects with ≥ 6-point increase in COWS within the first 6, 12, 24, or 48 hours post SUBLOCADE administration will be summarized using the FAS. As this is a cumulative endpoint, once a subject has a ≥ 6-point increase in COWS, the subject will be counted for that timepoint and all subsequent timepoints. The denominator at each timepoint will be the number of subjects who have a pre-SUBLOCADE COWS assessment and either 1) have a ≥ 6-point increase in COWS at or before the timepoint, or 2) have at least one post-SUBLOCADE COWS assessment within the timepoint interval. COWS assessments occurring at unscheduled visits will be included in the derivation.

The AUC will be calculated using the linear trapezoidal method, i.e.,

$$AUC = \frac{1}{2}\sum_{i=0}^{n} (T_{i+1} - T_i)(C_{i+1} - C_i)$$

where T_i is the i^{th} time value, C_i is the i^{th} COWS score, and n is the number of time values. Inherent to this formula, missing COWS scores are imputed in a linear manner.

The area under the curve (AUC) of COWS score from the time of administration of SUBLOCADE (i.e., time 0) through 6, 12, 24 and 48 hours after SUBLOCADE administration will be calculated using the FAS, and summarized using descriptive statistics for continuous endpoints (e.g., n, mean, median, SD, minimum and maximum).

The total score on the COWS and opioid craving visual analogue scale (OC-VAS) during the treatment period (i.e. at each assessment timepoint from administration of TM buprenorphine at Day 1 through EOT) will be summarized using descriptive statistics for continuous endpoints for the absolute value and change from the pre-TM Buprenorphine and pre-SUBLOCADE values. The analysis will use the FAS and observed data.

14.4.2 Exploratory Endpoints

The number and percentage of subjects who experience precipitated withdrawal from TM buprenorphine (defined as an increase in COWS by ≥6 from prior to the most recent dose of TM buprenorphine before SUBLOCADE administration) will be summarized using the TM Buprenorphine analysis set. The number, percentage and its 2-sided 95% exact CI using binomial distribution (Clopper-Pearson method) will be constructed using observed data.

Peak and overall plasma exposure to NMP following a single SC injection of 300 mg SUBLOCADE will be evaluated. The following PK parameters for NMP will be derived by non-compartmental analysis:

- C_{max}: maximum observed plasma concentration
- T_{max}: time of maximum observed plasma concentration
- AUC_{last}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule.
- AUC_{inf}: area under the plasma concentration-time curve from time 0 extrapolated to infinite time.

Analysis may include calculation of other PK parameters as applicable. Pharmacokinetic calculations will be performed using WinNonlin Phoenix version 6.3 or higher (Pharsight Corporation). The exploratory PK endpoints will be analysed using the PK analysis set.

A more complete description of the PK analyses will be provided in the SAP.

Plasma concentrations of NMP and the computed plasma PK parameters of NMP will be listed and summarised. Individual and mean plasma concentration versus time plots will be presented on linear and semi-logarithmic scales. Summary statistics (number of observations, mean, SD, minimum, maximum, geometric mean and coefficient of variation) for all relevant PK parameters of NMP will be presented.

14.5 Analysis of Other Safety Assessments

Other safety assessments data will be analysed using the safety population, descriptive statistics for continuous endpoints (e.g., n, mean, median, SD, minimum and maximum), and frequency counts with percentages for discrete endpoints. Complete details of the safety analyses will be provided in the SAP.

14.5.1 Adverse Events

Adverse events will be coded using the most up-to-date version of the MedDRA dictionary and grouped by primary system organ class. The Investigator determines the intensity of AEs and the relationship of AEs to study therapy.

A TEAE is defined as an AE observed after starting administration of TM buprenorphine. If subject experiences an event both prior to starting administration of TM buprenorphine and ongoing during the treatment, the event will be considered a TEAE (of the treatment) only if it has worsened in severity (i.e., it is reported with the date of worsening as the new start date/time) after starting administration of the buprenorphine.

All TEAEs collected during the treatment period will be presented by system organ class and preferred term, each in descending order of frequency, unless otherwise specified. Treatment-emergent AEs, drug-related TEAE, serious TEAE, drug-related serious TEAE and TEAE leading to treatment discontinuation will be summarised by system organ class and preferred term; TEAEs will also be summarised intensity, system organ class and preferred term.

14.5.2 Vital Signs

The results of scheduled assessments of vital signs, including absolute values and change from the pre-SUBLOCADE value will be summarised at each time point, with number of subjects (n), mean, SD, median, minimum and maximum values.

14.5.3 Electrocardiogram

At each time point, absolute values and change from the pre-SUBLOCADE value of ECG numeric variables will be summarised with n, mean, SD, median, minimum and maximum values. A shift table of the Investigator's assessment of the ECG results compared pre-SUBLOCADE values will be presented using the following categories: Normal; Abnormal, NCS; Abnormal, clinically significant; or Missing. The number and percentage of each cross-classification group of the shift table will be presented. Subject with missing pre-SUBLOCADE or Post- SUBLOCADE will be not included for percentage calculation.

14.5.4 Clinical Laboratory Tests

At each time point, absolute values and change from the pre-SUBLOCADE value of clinical laboratory variables will be summarised with n, mean, SD, median, minimum and

maximum values if the tests were performed at both pre-SUBLOCADE and EOT (e.g., serum chemistry, etc.). All laboratory data (including re-check values if present) will be listed chronologically.

14.5.5 Sedation Visual Analogue Scale

At each time point, absolute values and change from the pre-SUBLOCADE value of Sedation VAS will be summarised with n, mean, SD, median, minimum and maximum values.

14.5.6 Other Safety Variables

The results of scheduled assessments of pregnancy tests, medical/psychiatric history, substance/drug use history, concomitant medications and liver function will be summarised and listed. Further details will be provided in the SAP.

14.6 Demographic and Baseline Characteristics

Demographic and disease characteristics at screening, (e.g., age, gender, race, ethnicity, weight, height, BMI, tobacco use, alcohol use and drugs of abuse, baseline disease history) will be summarised for FAS and safety population using descriptive statistics. Qualitative variables, (e.g., gender, race) will be summarised using frequencies; quantitative variables, (e.g., age, weight, height) will be summarised using (n, mean, SD, median, minimum and maximum).

14.7 Handling of Missing Data

As described in Section 14.4, for the analyses of change in COWS ≥ 6, observed COWS data will be used with no imputation. However, the cumulative summaries by definition carry forward a previous occurrence of COWS ≥ 6.

For the analyses of absolute scores and changes in COWS total score and OC-VAS score, observed COWS and OC-VAS data will be used with no imputation. The AUC derivation for the COWS scores imputes missing scores in a linear manner.

14.8 Interim Analysis

No formal interim analyses are planned for this study.

15 ETHICS AND RESPONSIBILITIES

15.1 Good Clinical Practice

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

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

15.2 Data and Safety Monitoring Committee

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

15.3 Institutional Review Board/Independent Ethics Committee

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

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

15.4 Informed Consent

The Investigator or a person designated by the Investigator (if allowed by local regulations) is to obtain written informed consent 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 prior to presenting them to a potential participant.

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

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.

15.5 Study Files and Record Retention

The Investigator must maintain all study-related records (except for those required by local regulation to be maintained elsewhere) in a safe and secure location throughout the conduct and following the closure of the study. The records must be accessible upon request (e.g., for an IRB, Indivior or regulatory inspection) along with the facility, study personnel and supporting systems/hardware. All documents pertaining to the study, including all versions of the approved study protocol, copy of the ICF and other documents as required per local laws and regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] documents), completed eCRFs, 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. If the Investigator withdraws from the study (e.g., relocation, retirement) all study-related records should be transferred, in a written agreement with Indivior, to a mutually agreed upon designee within Indivior-specified time frame.

16 AUDITING AND MONITORING

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

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

The clinical monitor(s) will contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel. In accordance with applicable regulations and GCP guidelines, the Investigator shall make available for

direct access all study-related records upon request by Indivior, Indivior's agents, clinical monitor(s), auditors and/or IRB. The monitors will visit the site during the study in addition to maintaining frequent telephone and written communication. The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity and enrolment rate.

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

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

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

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

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

17 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Indivior. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB 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 and the Investigator must await approval before implementing the changes. Indivior or designated representative will submit substantial protocol amendments to the appropriate Regulatory Authorities for approval.

If in the judgment of the IRB, the Investigator and/or Indivior, 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 determination.

18 STUDY REPORT AND PUBLICATIONS

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

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

19 STUDY DISCONTINUATION

Both Indivior and the Investigator reserve the right to terminate the study at the Investigator's site at any time. Should this be necessary, Indivior, or a specified designee will inform the appropriate Regulatory Authorities of the termination of the study and the reasons for its termination, and the Investigator will inform the IRB of the same. In terminating the study, Indivior and the Investigator 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 and Indivior personnel (or their representatives) will be allowed full access to inspect and copy the records. All subject bodily fluids and/or other materials collected shall be used solely in accordance with this protocol and the ICF signed by the subject, unless otherwise agreed to in writing by Indivior.

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 clinic without first redacting subject identifiers.

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22 APPENDIX 1

Cytochrome P450 3A4 Inhibitors			
Name	**Example Brand Name(s)**	**Name**	**Example Brand Name(s)**
Amiodarone	Cordarone, Nexterone	Ketoconazole	Nizoral
Amprenavir	Agenerase,	Metronidazole	Flagyl
Aprepitant	Emend	Mibefradil	Posicor
Chloramphenicol	Chloromycetin	Miconazole	Oravig
Cimetidine	Tagamet	Mifepristone	Mifeprex, Korlym
Ciprofloxacin	Ciloxan, Cipro	Nefazodone	Serzone
Clarithromycin	Biaxin	Nelfinavir	Viracept
Clotrimazole	Lotrimin	Nicardipine	Cardene
Cyclosporine	Neoral, Sandimmune	Norfloxacin	Noroxin
Delavirdine	Rescriptor	Norfluoxetine	Seproxetine (discontinued)
Diethyl-dithiocarbamate	(zinc chelator used in cancer, no other name)	Propofol	Diprivan
Diltiazem	Cardizem, Dilacor	Quinine	Qualaquin
Ethinyl estradiol	Apri, Aviane, Beyaz	Ritonavir	Norvir
Erythromycin	Erythrocin	Saquinavir	Invirase
Fluconazole	Diflucan	Sertraline	Zoloft
Fluoxetine	Prozac	Starfruit	Carambola, fruit of Averrhoa carambola
Fluvoxamine	Luvox	Telithromycin	Ketek
Grapefruit juice	Grapefruit juice	Verapamil	Isoptin
Imatinib	Gleevec	Voriconazole	Vfend
Indinavir	Crixivan	Zafirlukast	Accolate

Cytochrome P450 3A4 Inhibitors			
Name	**Example Brand Name(s)**	**Name**	**Example Brand Name(s)**
Itraconazole	Sporanox		

Cytochrome P450 3A4 Inducers			
Name	**Example Brand Name(s)**	**Name**	**Example Brand Name(s)**
Barbiturates	Nembutal, Luminal	Phenytoin	Dilantin, Phenytek
Carbamazepine	Carbatrol, TEGretol	Pioglitazone	Actos
Dexamethasone	Decadron	Primidone	Mysoline
Efavirenz	Sustiva, Atripla	Rifabutin	Mycobutin
Ethosuximide	Zarontin	Rifampin	Rifadin, Rimactane
Glucocorticoids	Prednisone, Medrol, Millipred	Hypericum perforatum	Medicinal herb
Glutethimide	Elrodorm, Noxyron.	Sulfinpyrazone	Anturane
Modafinil	Provigil		
Nevirapine	Viramune		
Oxcarbazepine	Trileptal, Oxtellar XR		
Phenobarbital	Luminal		

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