PROTOCOL

STUDY NUMBER: INDV-6000-404

PROTOCOL TITLE: An Open-label treatment extension study for eh Rapid Initiation of Extended-Release Buprenorphine Subcutaneous Injection (SUBLOCADE™)

NCT NUMBER: NCT04060654

DATE: 04Dec2019

16.1.1 CLINICAL RESEARCH PROTOCOL

DRUG:	SUBLOCADE™ (extended-release buprenorphine)
STUDY NUMBER:	INDV-6000-404
PROTOCOL TITLE:	**An Open-label, treatment extension study for the Rapid Initiation of Extended-Release Buprenorphine Subcutaneous Injection** (SUBLOCADE™)
SHORT TITLE:	SUBLOCADE Rapid Initiation Extension Study
IND NUMBER:	107,607
PHASE:	IV
SPONSOR:	Indivior Inc. 10710 Midlothian Turnpike, Suite 125 North Chesterfield, VA 23235 USA
ORIGINAL PROTOCOL DATE:	07 August 2019
PROTOCOL AMENDMENT 1 DATE:	04 December 2019

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: An Open-label, treatment extension study for the Rapid Initiation of Extended-Release Buprenorphine Subcutaneous Injection (SUBLOCADE™)

Study No: INDV-6000-404

Protocol Amendment 1 Date: 04 December 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: 4-Dec-2019
DD-MMM-YYYY
[redacted]
Indivior Medical Monitor
Indivior Inc.

Signed: [redacted] Date: 4 Dec 2019
DD-MMM-YYYY
[redacted]
Senior Vice President, Global Medicines Development
Indivior Inc.

INDV-6000-404: AN OPEN-LABEL, TREATMENT EXTENSION STUDY FOR THE RAPID INITIATION OF EXTENDED-RELEASE BUPRENORPHINE SUBCUTANEOUS INJECTION (SUBLOCADE™)

PROTOCOL AMENDMENT 1

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: 06-DEC-2019
DD-MMM-YYYY

Printed Name and Credentials:	[redacted]
Title:	PI / MEDICAL DIRECTOR
Clinic Name:	[redacted]
Telephone:	[redacted]
Address:	[redacted]

SUMMARY OF CHANGES

	Change	Section Affected	Summary of Change(s)
1.	Number of subjects increased from up to 15, to 25.	Section 4.1 Section 5.1 Section 14.2	Number of subjects increased to account for additional subjects enrolled onto INDV-6000-403 study.
2.	Concomitant medications or indications for such, will not be coded or summarized.	Section 13.1 Section 14.4.3	Concomitant medications are required to be listed only for this study.
3.	Detox and MOUD history will be collected and summarized.	Section 4.1 Section 4,2 Section 8.1 Section 14.4.3	This will be collected retrospectively for subjects enrolled in the study at the time of this amendment.
4.	Added that the safety population will be the primary population for all analyses.	Section 14.3	The safety population was defined but utilization for analyses not stated.
5.	Typographical error corrected.	Section 4.2	Injection 3 Visit, corrected to “Visit 3”
6.	Typographical error corrected.	Section 9.8	Subjects do not “check-in” to the clinic on day 1, therefore text updated to state subjects abstain from alcohol throughout the study.

STUDY PERSONNEL INFORMATION

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

STUDY SUMMARY

Protocol Number:	INDV-6000-404
Title:	An Open-label, treatment extension study for the Rapid Initiation of Extended-Release Buprenorphine Subcutaneous Injection (SUBLOCADE™)
Rationale:	This study (INDV-6000-404) is to provide ongoing treatment with SUBLOCADE for up to 5 additional injections and safety monitoring for subjects who initiated SUBLOCADE following a single dose of transmucosal (TM) buprenorphine in study INDV-6000-403.
Target Population:	Subjects with moderate or severe opioid use disorder (OUD) who are seeking medication for OUD (MOUD) and have completed INDV-6000-403 study.
Number of Subjects:	Up to 25 adult subjects
Objective:	The objective of this study is to assess the longer-term safety of an abbreviated initiation protocol of SUBLOCADE in subjects who have completed INDV-6000-403. It is also to provide treatment to these individuals while they seek longer-term care arrangements, as it (on average) takes an individual with OUD 6 months between seeking treatment and achieving an appointment at a provider within the US.
Study Design:	Only subjects who have completed the End of Treatment (EOT) procedures for Study INDV-6000-403, have signed the INDV-6000-404 informed consent form (ICF), and meet all the enrollment criteria may be considered for inclusion in this study. The INDV-6000-403 EOT visit is 28 days after the subject's first dose of SUBLOCADE in INDV-6000-403, therefore the INDV-6000-403 EOT and the INDV-6000-404 screening and Day 1 visit for this study will occur within 2 days, thus the INDV-6000-403 EOT assessments will serve as the screening assessments for the Screening Visit (Day 1) of this study.

Any AEs and concomitant medications ongoing at the INDV-6000-403 EOT will be re-recorded for this study. In addition, demographics, height, medical/psychiatric, substance and drug of abuse history will not be re-collected and will be taken from the INDV-6000-403 screening assessments. A detailed detox and MOUD treatment history will be collected at screening. For those subjects who have enrolled in the study prior to approval of protocol amendment 1, their detox and MOUD treatment history will be collected retrospectively at their next visit.

On Day 1, eligible subjects will receive a SC injection of 300mg SUBLOCADE. Before departing the site, any new adverse events (AEs) or concomitant medications will be recorded.

Subjects will return to the site for monthly injection visits every 4 weeks (-2 / +7 days) for a total of up to 5 injections. At Injection Visits 2 through 5, subjects will be evaluated in accordance with local standard of care and results for the following procedures will be recorded: urine pregnancy test (to be performed before SUBLOCADE administration for all female subjects who are of childbearing potential); urine drug screen (UDS) and evaluation of previous injection site for potential reaction and evidence of attempts to remove the depot. For injections 2 to 5, subjects may receive either a dose of 100 mg SUBLOCADE or 300 mg SUBLOCADE, based on the medical judgment of the Investigator, per the SUBLOCADE USPI. During each visit the subject will be assessed for AEs and use of concomitant medications.

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/ET visit 4 weeks after SUBLOCADE administration.
At the EOT/ET Visit, results for the following procedures and assessments will be recorded: urine pregnancy test for all female subjects who are of childbearing potential; evaluation of previous injection site for potential reaction and evidence of attempts to remove the depot; UDS; use of concomitant medications and assessment for AEs. At every Visit options for continued care should be discussed with the subject.

	Any subject with ongoing AEs or concomitant medications at the EOT Visit will also be followed up by telephone 4 weeks later for a safety follow up to assess the ongoing AEs or concomitant medications only.
Primary Endpoint:	The proportion of subjects with treatment emergent adverse events (TEAEs) at any time during the treatment period.
Other Safety Assessments:	Additional safety endpoints will include assessment of: drug-related TEAEs, serious TEAEs, drug-related serious TEAEs, TEAEs leading to treatment discontinuation and concomitant medications.

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LIST OF TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
BMI	body mass index
CRF	case report form
EOT	end of treatment
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MAOI	monoamine oxidase inhibitor
MOUD	Medication for Opioid Use disorder
NNRTI	non-nucleoside reverse transcriptase inhibitor
NMP	N-methyl-2-pyrrolidone
OUD	opioid use disorder
PLGH	poly(DL-lactide-co-glycolide) with a carboxylic acid end group
QA	quality assurance
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
TM	Transmucosal
UDS	urine drug screen
ULN	upper limit of normal
USPI	United States Prescribing Information
WHO	World Health Organization

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. Medications for OUD (MOUD) are recommended by treatment guidelines as the current standard of care for OUD (Kampman 2015), combined with counselling/behavioural therapy 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 buprenorphine. After initial formation of the depot, buprenorphine is released via diffusion from, and the biodegradation of, the depot.

See SUBLOCADE USPI for further information.

1.2 Study Rationale

Currently, patients who are appropriate candidates for SUBLOCADE must initiate treatment with transmucosal (TM) buprenorphine for a minimum of 7 days before receiving their first injection (SUBLOCADE United States Prescribing Information [USPI]). Study INDV-6000-403 is being conducted to evaluate the safety and tolerability of starting SUBLOCADE treatment following a shorter period of TM buprenorphine treatment. This study (INDV-6000-404) is to provide ongoing treatment with SUBLOCADE for up to 5 additional injections and safety monitoring for subjects who initiated SUBLOCADE following a single dose of transmucosal (TM) buprenorphine in study INDV-6000-403.

1.2.1 Dosing Regimen

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

The recommended initial dose of SUBLOCADE is 300mg monthly for the first 2 injections of treatment. Subjects have received 1 x 300mg SUBLOCADE injection in the

INDV-6000-403 study, therefore subjects must receive 300mg SUBLOCADE for the first injection of this study. Subjects may receive either 100 mg or 300 mg SUBLOCADE for the maintenance dose (all subsequent injections), based on the medical judgment of the Investigator as per the SUBLOCADE USPI.

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 when used as directed. For this extension study, SUBLOCADE will be administered as recommended in the SUBLOCADE USPI.

1.3.1 Risk Assessment

The safety profile of buprenorphine is well-established, and the AE profile of buprenorphine is well characterised. Commonly reported treatment-emergent 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 subcutaneous) in multiple countries and by various manufacturers. Buprenorphine extended-release SC injection was approved as a monthly treatment for OUD in 2017 (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.

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 subjects will receive limited benefit from participation in the single-dose (of SUBLOCADE) study (INDV-6000-403), participation in the combined INDV-6000-403 and INDV-6000-404 studies will allow more meaningful engagement with MOUD and the results could provide support for more rapid SUBLOCADE initiation, which is expected to improve treatment compliance, engagement and retention in treatment. 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 dose dependently inhibit fentanyl-induced respiratory depression. Being able to initiate treatment-seeking patients with SUBLOCADE on the 1st day of treatment may therefore help 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 extension of the single dose study (INDV-6000-403) to evaluate a more rapid treatment initiation protocol for SUBLOCADE in patients with OUD.

2 STUDY OBJECTIVE

The objective of this study is to assess the longer-term safety of an abbreviated initiation protocol of SUBLOCADE in subjects who have completed INDV-6000-403. It is also to provide treatment to these individuals while they seek longer-term care arrangements, as it (on average) takes an individual with OUD 6 months between seeking treatment and achieving an appointment at a provider within the US.

3 STUDY ENDPOINTS

3.1 Primary

The proportion of subjects with treatment emergent adverse events (TEAEs) at any time during the treatment period (i.e., any time after administration of SUBLOCADE).

3.2 Other Safety Assessments

Additional safety endpoints will include assessment of: drug-related TEAEs, serious TEAEs, drug-related serious TEAEs, TEAEs leading to treatment discontinuation and concomitant medications.

4 STUDY PLAN

4.1 Study Design

This is a single center, open-label, SUBLOCADE treatment extension study in which up to 25 subjects diagnosed with moderate or severe OUD will be enrolled. A subject is defined as enrolled when the first dose of SUBLOCADE is administered for this study.

Only subjects who have completed the End of Treatment (EOT) procedures for Study INDV-6000-403, have signed the INDV-6000-404 informed consent form (ICF), and meet all the enrollment criteria may be considered for inclusion in this study.

The INDV-6000-403 EOT visit is 28 days after the subjects first dose of SUBLOCADE in INDV-6000-403, therefore the INDV-6000-403 EOT and the INDV-6000-404 screening and Day 1 visit for this study will occur within 2 days.

The ICF may be shared with the potential subject before the INDV-6000-403 EOT Visit to discuss this study as a possible treatment option. However, the ICF must not be signed until all assessments for the INDV-6000-403 EOT Visit are complete.

The INDV-6000-403 EOT assessments will serve as the screening assessments for the Screening Visit (Day 1) of this study. Any AEs and concomitant medications ongoing at the INDV-6000-403 EOT will be re-recorded for this study. In addition, demographics, height, medical/psychiatric, substance and drug of abuse history will not be re-collected and will be taken from the INDV-6000-403 screening assessments. A detailed detox and MOUD treatment history will be collected at screening. For those subjects who have enrolled in the study prior to approval of protocol amendment 1, their detox and MOUD treatment history will be collected retrospectively at their next visit.

On Day 1, eligible subjects will receive a SC injection of 300mg SUBLOCADE.

Before departing the site, any new adverse events (AEs) or concomitant medications will be recorded.

Subjects will return to the site for monthly injection visits every 4 weeks (-2 / +7 days) for a total of up to 5 injections. At Injection Visits 2 through 5, subjects will be evaluated in accordance with local standard of care and results for the following procedures will be recorded: urine pregnancy test (to be performed before SUBLOCADE administration for all female subjects who are of childbearing potential); urine drug screen (UDS) and evaluation of previous injection site for potential reaction and evidence of attempts to remove the depot. For injections 2 to 5, subjects may receive either a dose of 100 mg SUBLOCADE or 300 mg SUBLOCADE, based on the medical judgment of the Investigator, per the SUBLOCADE USPI. During each visit the subject will be assessed for AEs and use of concomitant medications.

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/ET visit 4 weeks after SUBLOCADE administration.
At the EOT/ET Visit, results for the following procedures and assessments will be recorded: urine pregnancy test for all female subjects who are of childbearing potential; evaluation of previous injection site for potential reaction and evidence of attempts to remove the depot; UDS; use of concomitant medications and assessment for AEs. At every Visit options for continued care should be discussed with the subject.

Any subject with ongoing AEs or concomitant medications at the EOT Visit will also be followed up by telephone 4 weeks later for a safety follow up to assess the ongoing AEs or concomitant medications only.

4.2 Schedule of Assessments

An overview of the schedule of assessments for the study is provided in Table 1.

Table 1 Schedule of Assessments – Overview of Study

Procedure/Assessment	Screening	Injection 1	Injection 2	Injection 3	Injection 4	Injection 5	ET / EOT[9]	Safety Follow up[10]
Visit Number	**1**		**2**	**3**	**4**	**5**	**6**	**7**
Day(s)		**1**	**29**	**57**	**85**	**113**	**141**	**169**
Window (days)		**+2**	**-2 / +7**	**-2 / +7**	**-2 / +7**	**-2 / +7**	**-2 / +7**	**-7 / +7**
Informed Consent[1]	X							
Inclusion/Exclusion Criteria	X							
Demographics[2]	403[2]							
Medical/Psychiatric History[2]	403[2]							
Substance/Drug Use History[2]	403[2]							
Height[2]	403[2]							
Weight/BMI[3]	403 EOT[3]							
Urine Pregnancy Test[5]	403 EOT[3]		X	X	X	X	X	
UDS[6]	403 EOT[3]		X	X	X	X	X	
Injection Site Evaluation[7]	403 EOT[3]		X	X	X	X	X	
AE Assessment	X[4]		X	X	X	X	X	
Concomitant Medications	X[4]		X	X	X	X	X	X
Study Drug Administration		X	X	X	X	X		
MOUD and treatment History[11]	X							
Counselling[8]	X							

AE=adverse event; BMI=body mass index; EOT=End-of-Treatment; ET=Early Termination; OUD=opioid use disorder; UDS=urine drug screen; MOUD=medication for opioid use disorder

1. Written informed consent must be obtained after completion of all INDV-6000-403 EOT procedures and before any INDV-6000-404 study-specific assessments/procedures are initiated.
2. This data will not be re-collected; the data from the INDV-6000-403 screening visit will be used.

3. This data will not be re-collected; the data from the INDV-6000-403 EOT visit will be used.
4. Any ongoing (at the INDV-6000-403 EOT) or new AEs or concomitant medications in this study will be recorded.
5. Required for female subjects of childbearing potential only, to be performed before SUBLOCADE dosing at Visits 1 to 6.
6. Qualitative test to be performed before SUBLOCADE dosing at Visits 1 to 6.
7. Injection site will be evaluated for signs of attempted removal before SUBLOCADE dosing at Visits 1 to 6. Any injection site reactions or infections will be recorded as AEs.
8. All subjects will receive counselling as determined by local standard of care throughout the study from Day 1 through EOT.
9. All subjects who receive SUBLOCADE (including those who wish to discontinue early), will be encouraged to attend the EOT visit 4 weeks after SUBLOCADE administration.
10. Any subject with ongoing AEs or concomitant medications at the EOT/ET Visit will also be followed up by telephone 4 weeks later for a safety follow up to assess the ongoing AEs or concomitant medications only.
11. A detailed detox and MOUD treatment history will be collected at screening. For those subjects who have enrolled in the study prior to approval of protocol amendment 1, their detox and MOUD treatment history will be collected retrospectively at their next visit.

5 POPULATION

5.1 Number of Subjects

Up to 25 adult subjects with moderate or severe OUD who are seeking MOUD and have completed the EOT Visit for the INDV-6000-403 study are planned to be enrolled into the study.

5.2 Inclusion Criteria

Subjects must meet all the following criteria to be eligible for the study:

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

2. Completed the EOT Visit for the INDV-6000-403 Study.

3. Is an appropriate candidate in the opinion of the Investigator or medically qualified sub-Investigator.

5.3 Exclusion Criteria

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

1. Subject compliance issues during participation in the INDV-6000-403 study which, in the opinion of the Investigator, could potentially compromise subject safety.

2. 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.

5.4 Subject Screening

Subjects who provide written informed consent will have their INDV-6000-403 assessments (per Table 1) re-reviewed to confirm study eligibility.

5.5 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; the same subject identification number from INDV-6000-403 will be 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 Enrolled

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

6.3 Not Enrolled

A subject will be considered not enrolled if written informed consent is obtained but the subject does not receive SUBLOCADE. Reasons for not enrolling (e.g., withdrawal of consent, does/not meet specified inclusion or exclusion criteria) will be recorded in the case report form (CRF).

6.4 Treatment Period

Treatment period begins when the SUBLOCADE injection is given on Day 1 and ends after all assessments have been made at the EOT Visit.

6.5 Treatment Period Completion

A subject will be considered as completing the treatment period if they have received Injection 1 and Injection 5.

6.6 Study Completion

A subject will be considered to have completed the study if they have completed the last injection visit (Injection 5) and the scheduled EOT visit.

6.7 Early Termination

A subject will be considered an Early Termination if he/she is dosed with SUBLOCADE and does not complete the study (did not complete the last injection visit [Injection 5]) and the scheduled EOT visit.

Reasons for early termination (e.g., withdrawal of consent, lost to follow up, identification / move to alternative treatment site) will be recorded in the CRF. Subjects who Early Terminate from the study will be encouraged to attend the ET visit 4 weeks after SUBLOCADE administration, as well as a safety follow up via telephone if any AEs and concomitant medications are ongoing at the time of the ET visit.

6.8 Withdrawal and Stopping Criteria

6.8.1 Subject Withdrawal from the Study

If the subject has 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 CRF (e.g., subject is lost to follow-up, Indivior terminates the study or Investigator's discretion).

6.8.2 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).

6.8.3 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 subjects will be evaluated in accordance with local standard of care, and only results for study specific assessments and procedures will be recorded in the CRF. Study assessments and procedures, including the timing of assessments, are summarised in Table 1. Further details on safety assessments are provided in Section 8.2.

A signed written ICF must be obtained from the subject before any study assessments or procedures may be performed. All assessments and procedures may be performed more frequently, if clinically indicated.

8.1 Demographics and Medical/Psychiatric History

A detailed medical and psychiatric history was collected during the INDV-6000-403 study and will not be re-collected. A detailed detox and MOUD treatment history will be collected at screening. For those subjects who have enrolled in the study prior to approval of protocol amendment 1, their detox and MOUD treatment history will be collected retrospectively at their next visit.

8.2 Safety Assessments

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

8.2.1 Clinical Laboratory Tests

Clinical laboratory tests for Virology, Haematology, Serum Chemistry and Urinalysis were collected during the INDV-6000-403 study and will not be re-collected.

8.2.1.1 Urine Drug Screening (UDS)

A qualitative UDS will be conducted at each Visit, as per the schedule of events in Table 1. The UDS will include the following substances:

- Opioids
- Oxycodone
- Morphine
- Fentanyl
- Methadone
- Cocaine
- Amphetamines
- Cannabinoids
- Barbiturates
- Benzodiazepines
- Methamphetamine
- Phencyclidine

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

8.2.1.2 Urine Pregnancy Test

A urine pregnancy test will be performed at each visit using a licensed test (dipstick), for females of child bearing potential only.

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

8.2.2 Injection site Evaluation

The Injection site will be evaluated for signs of attempted removal before dosing with SUBLOCADE at each visit, as shown in Table 1. Any attempts at a SUBLOCADE depot removals by the subject should be reported as an AE, and any removals should be reported as an AE of Special Interest, see Section 10.7. Any injection site reactions or infections will be recorded as AEs.

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 study drug, SUBLOCADE, will be provided by the Sponsor in two strengths 100mg and 300mg buprenorphine.

9.1 Description

9.1.1 Formulation

SUBLOCADE is a colourless to amber sterile solution for SC injection designed to deliver a buprenorphine dose 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.

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

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.

SUBLOCADE should be administered as per the instructions for use in the SUBLOCADE USPI. The recommended initial dose of SUBLOCADE is 300mg monthly for the first 2 injections of treatment. Subjects have received 1 x 300mg SUBLOCADE injection in the INDV-6000-403 study, therefore subjects must receive 300mg SUBLOCADE for the first injection of this study.

Subjects may receive either 100 mg or 300 mg SUBLOCADE for the maintenance dose (all subsequent injections), based on the medical judgment of the Investigator as per the SUBLOCADE USPI. Reasons for dose adjustments should be recorded in the source and CRF.

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 CRF.

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. 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 (including ongoing concomitant medications recorded at the INDV-6000-403 EOT) until the INDV-6000-404 EOT at the time points listed in Table 1. Any subject with ongoing concomitant medications at the INDV-6000-404 EOT will be followed up by telephone 4 weeks later for a safety follow up 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 CRF. 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 alcohol 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.

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

Supplemental buprenorphine 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 CRF.

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 CRF. Likewise, surgical removal by a physician will be documented in the source and recorded in the CRF. 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, documented in the source and recorded in the CRF.

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 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, an AE of special interest is any occurrence of a SUBLOCADE depot removal (see Section 10.7); Subjects with alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (> 35% direct) are defined as SAEs of special interest.

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

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.

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 (including ongoing AEs at the INDV-6000-403 EOT) until completion of the EOT visit. Any subject with ongoing AEs at the INDV-6000-404 EOT will be followed up by telephone 4 weeks later for a safety follow up to assess the ongoing AEs.

Subjects with ongoing SAEs at the safety follow up 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 safety follow up 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

Clinical Laboratories are not collected for this study. However, if an Investigator performs these tests as part of the local standard of care the results may be considered a reportable AE 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.

If a subject experiences any of the below Liver Chemistry criteria the Indivior medical monitor should be notified to discuss the subject's course of action:

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.

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).

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: PatientSafetyNA@indivior.com
Fax: (804) 423-8951

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 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) between scheduled visits, the subject will be asked to return to the clinic at the next scheduled visit. Removal of the SUBLOCADE depot will not be required if pregnancy occurs.

If a urine pregnancy test during a subject's visit confirms that a subject is pregnant, the subject will receive no further injections, and the current visit will be considered the subject's ET Visit. If the subject any ongoing AEs or concomitant medications at the ET Visit, she will also be followed up by telephone 4 weeks later for the safety follow up to assess the ongoing AEs or concomitant medications only.

The Investigator should fully inform the female subject of the potential risk to the foetus.

13 DATA MANAGEMENT

13.1 Data Collection and Management

Data will be entered onto a CRF and will be managed in accordance with the data management plan to ensure that the integrity of the data is maintained. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).. 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 CRFs will be reviewed and checked for omissions, apparent errors and values requiring further clarification using manual procedures. Data queries requiring clarification will be generated and addressed by the investigational site. Only authorized personnel will make corrections to the CRFs, 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 CRF. The data recorded should be a complete and accurate account of the subject's record collected during the study.

Study data will not be recorded solely onto the CRF but will be initially documented in source documents. 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

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

14.1 General Procedures

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 safety follow up 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

Up to 25 adult subjects with moderate to severe OUD are planned to be enrolled onto the study.

14.3 Analysis Populations

The Safety population will consist of all subjects who received at least 1 dose of SUBLOCADE, and will be the primary population for all analyses

14.4 Analysis of Primary, Secondary and Exploratory Endpoints

14.4.1 Primary Endpoint

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.

A TEAE is defined as an AE observed after starting administration of SUBLOCADE in this study. If subject experiences an event both prior to starting administration of SUBLOCADE 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 SUBLOCADE in this study.

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.

14.4.2 Analysis of Other Safety Data

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.

Other safety data will be analysed using 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.

14.4.3 Other Safety Variables

The results of scheduled assessments of pregnancy tests and concomitant medications will be listed. Further details will be provided in the SAP.

Substance/drug use, detox and MOUD treatment history will be summarized and listed.

14.5 Demographic and Baseline Characteristics

Demographic and disease characteristics at screening, (e.g., age, gender, race, ethnicity, weight, height, Body Mass index (BMI), tobacco use, alcohol use and illicit drug use, baseline disease history) will be summarised 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).

14.6 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 CRFs, source records (subject records, subject diaries, hospital records, laboratory records, drug accountability records, etc.), and other study-related materials will be retained in the permanent archives of the study site.

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

The minimum retention time for retaining study records will be in accordance with the strictest standard applicable for the study site as determined by local laws, regulations or institutional requirements. 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 CRF completion will be provided and reviewed with study personnel before the start of the study. Indivior (or designee) will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to Indivior (or designee). Any discrepancies will be resolved with the Investigator or suitably qualified designee, as appropriate.

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

In accordance with the standards defined in Indivior SOPs and applicable regulatory requirements, clinical studies sponsored by Indivior are subject to Indivior Quality Assurance (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 CRFs with source documents. The Investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner. Full consultation with the Investigator will be made prior to and during such an audit, which will be conducted according to Indivior's or a contract research organisation's 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 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.

21 REFERENCES

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Substance Abuse and Mental Health Services Administration. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series. C. f. S. A. Treatment.40. 2004.

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Wiest K, Algera MH, Moss L, van Velzen M, Dobbins R. High Plasma Buprenorphine Concentrations Decrease Respiratory Effects of Intravenous Fentanyl. 50th Annual ASAM Conference. 2019.

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/