CLINICAL STUDY PROTOCOL: INDV-6000-405

Protocol Title: A Single-Dose Study to Evaluate the Relative Bioavailability, Safety, and Tolerability of SUBLOCADE at Alternative Injection Locations in Adults

Protocol Number: INDV-6000-405

Original Protocol Date: 18 Nov 2022

NCT: NCT05704543

TITLE PAGE

PROTOCOL TITLE: A Single-Dose Study to Evaluate the Relative Bioavailability, Safety, and Tolerability of SUBLOCADE at Alternative Injection Locations in Adults

Protocol Number: INDV-6000-405

Investigational New Drug (IND) Number: 107,607

Product: SUBLOCADE® (buprenorphine extended-release) injection

Brief Title: SUBLOCADE Alternative Injection Locations

Study Phase: IV

Sponsor Name: Indivior Inc.

Legal Registered Address:

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Approval Date: 18 Nov. 2022

Sponsor Signatories:

MEDICAL MONITOR NAME AND CONTACT INFORMATION

[redacted]

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

Protocol Number: INDV-6000-405

Protocol Title: A Single-Dose Study to Evaluate the Relative Bioavailability, Safety, and Tolerability of SUBLOCADE at Alternative Injection Locations in Adults

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

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

I agree to ensure all associates, colleagues, and employees delegated to assist with the conduct of the study are trained on this study protocol and amendments, 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 SUBOXONE and SUBLOCADE and appropriate information throughout the study. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

_____ _____

Signed Date: DD MMM YYYY

Printed Name and Credentials:	
Title:	
Site Number:	
Site Name:	
Telephone:	
Address:	

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve *(see also Table 7, Table 8, and Table 9)*
BLQ	below the lower limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
BUP	buprenorphine
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
C_{trough}	trough plasma concentration measured on Day 29
CPK	creatine phosphokinase
CRF	case report form
CRO	Contract Research Organisation
CSR	clinical study report
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
FDA	Food and Drug Administration

GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
INR	international normalised ratio
IRB	Institutional Review Board
IV	intravenous
IVRS/IXRS	Interactive Voice Response System
LDH	lactate dehydrogenase
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary For Regulatory Activities
MOUD	medicine for opioid use disorder
OUD	opioid use disorder
PK	pharmacokinetic(s)
PT	prothrombin time
PTT	activated partial thromboplastin time
QD	once daily
QTcF	heart rate-corrected QT interval (Fridericia's)
RBC	red blood cell (count)
SAE	serious adverse event

SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SoE	Schedule(s) of Events
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TM	transmucosal
T_{max}	time to maximum plasma concentration
UDS	urine drug screen
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WBC	white blood cell (count)
WHO	World Health Organization

PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Single-Dose Study to Evaluate the Relative Bioavailability, Safety, and Tolerability of SUBLOCADE at Alternative Injection Locations in Adults

Short Title: SUBLOCADE Alternative Injection Locations

Rationale: SUBLOCADE® (extended-release BUP injection) for SC use (CIII) is currently approved for SC administration in 4 different quadrants of the abdomen. Injection locations are rotated to minimise irritation.

Having 1 or more alternate injection sites is desirable in this patient population who may be taking SUBLOCADE for extended durations, based upon clinical response.

Data cited from literature suggests that the proposed alternative injection locations for SC administration are viable options for delivering similar PK properties: back of upper arm, buttocks, and thigh.

Objectives and Endpoints

Table 1 Objectives and Endpoints

Objective	Corresponding Endpoint
Primary	
• To assess the relative bioavailability of BUP when administered at alternative injection locations (test treatments), in comparison to the abdomen (reference treatment) following a single SC injection of SUBLOCADE in participants with OUD	• $AUC_{0\text{-}28days}$ and C_{max} for BUP
Secondary	
• To evaluate the safety and tolerability of SUBLOCADE when administered at alternative injection locations, in comparison to the abdomen	• Proportion of participants with TEAEs • Proportion of participants with TEAEs identified as injection site reactions • Proportion of participants with treatment-emergent SAEs • Injection site grading at 10 minutes and 2 hours post SUBLOCADE dosing • Injection Site Pain VAS at 1, 5, 10, 15, and 30 minutes post SUBLOCADE dosing

AUC=area under the curve; BUP=buprenorphine; C_{max}=maximum plasma concentration; OUD=opioid use disorder; SAE=serious adverse event; SC=subcutaneous; TEAE=treatment-emergent adverse event; VAS=visual analogue scale

Overall Design Synopsis

This is a multicentre, randomised, open-label, single-dose, parallel-group study in participants with moderate or severe OUD (based on criteria from the DSM-5 or documented history of moderate to severe OUD and receiving/stabilised on MOUD).

Brief Summary: The purpose of this study is to measure the relative bioavailability of BUP when administered at alternative injection locations in comparison to the abdomen following a single SC injection of SUBLOCADE in participants with OUD.

Participants will provide written informed consent before any protocol-related procedures commence. The study includes both a Residential (Inpatient) Period and a Non-Residential (Outpatient) Period.

Following Screening, all eligible participants must be stabilised on 12 mg SUBOXONE® (BUP/naloxone) sublingual film QD for a minimum of 7 days before the SUBLOCADE injection. Dose induction/stabilisation onto SUBOXONE may be completed as outpatient or inpatient, as necessary, according to the prescribing information for a maximum of 14 days before SUBLOCADE injection.

All participants will be admitted to the residential facility by the evening of Day -3.

The period from the first dose of SUBOXONE administered as part of this study through Day -1 will be referred to as the Run-in Period.

Following the Run-in Period, on Day 1, eligible participants will be randomised to a treatment arm.

Each treatment arm will receive a single, SC injection of 300 mg SUBLOCADE at a different injection location ie, abdomen (reference) or 1 of the alternative injection locations (test) ie, back of upper arm, buttocks, and thigh.

Safety measurements and blood samples for PK assessments during the Residential Period will be collected at scheduled time points until the participants are discharged from the residential facility on Day 3.

Participants will return to the clinical facility as outpatients for safety and PK assessments to be conducted according to the SoE until EOT.

Any participant with ongoing AEs at the EOT or ET visit will also be followed up by phone 2 weeks later for the EOS visit to assess any ongoing AEs and concomitant medications associated with those ongoing AEs only.

It is important that participants do not use any BUP-containing products, either therapeutically or illicitly during the course of the study. Such use would compromise the PK assessment of BUP and its metabolite, norbuprenorphine.

Number of Participants:

No formal statistical power analysis was performed to determine the sample size of this study. Based on historical experience from previous similar clinical trials, approximately 80 participants will be randomised in total, ideally to achieve 15 PK evaluable participants per each of the 4 treatment arms (injection locations): abdomen (reference), back of upper arm, buttocks, and thigh.

Note: *Screened* means participants' agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enroled, unless otherwise specified by the protocol. A participant will be considered enroled if the informed consent is not withdrawn prior to receiving the first dose of SUBOXONE film during run-in.

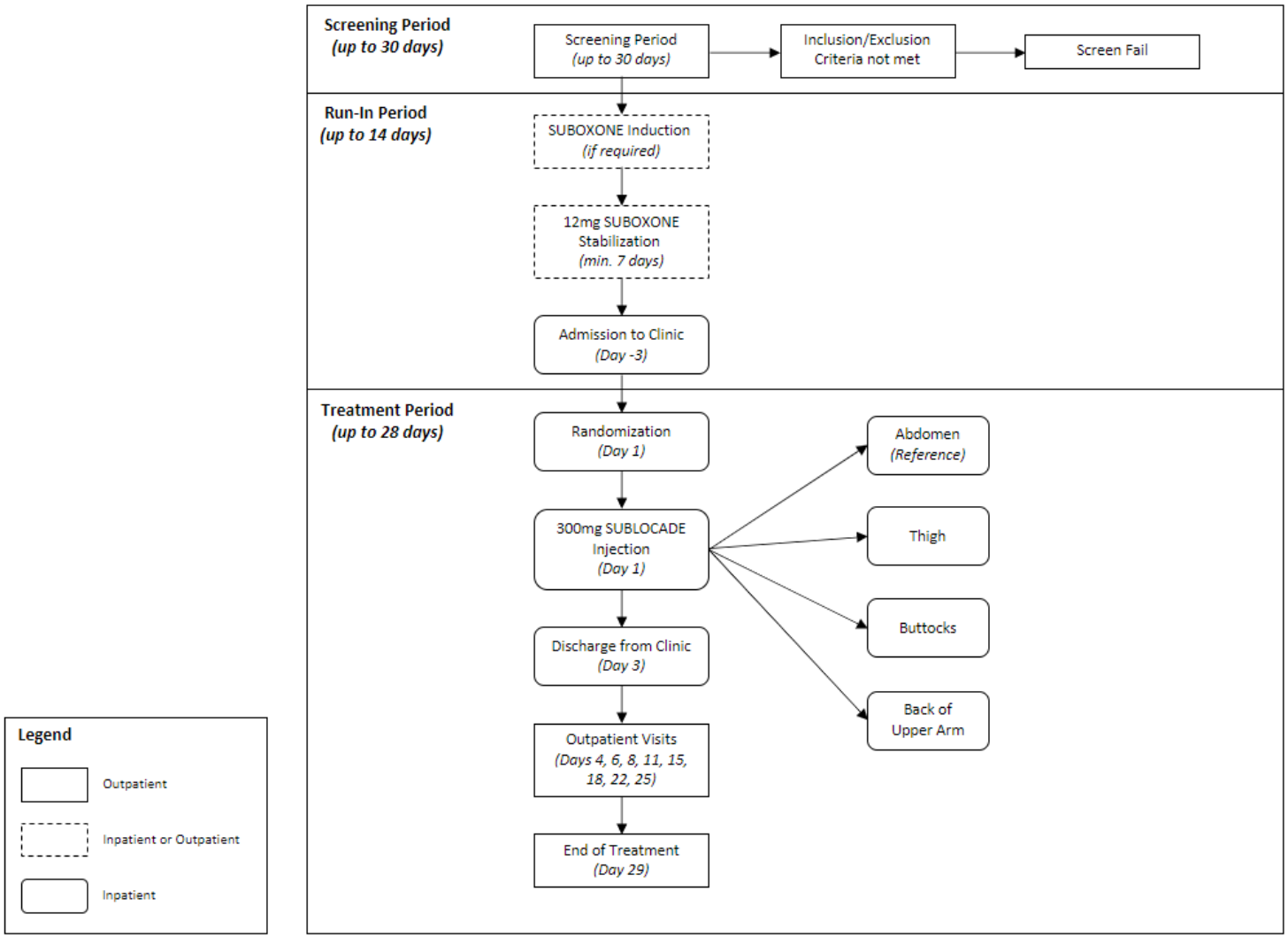
Study Duration:

The total duration of the study for each participant, including Screening, Run-in, Treatment, and Follow up, will be up to approximately 86 days, divided as follows:

- Screening: Up to 30 days
- Run-in Period: Up to 14 days
- Treatment Period: 28 days
- Follow-up Period: up to 14 days

1.2 Schema

Figure 1 Study Schema



1.3 Schedules of Events

See Section 10.6 for a detailed SoE for inpatient Day -3 to Day 3 with assessment windows.

Table 2 Schedule of Events – Screening to Day 3

		Inpatient/ Outpatient	Inpatient (See Section 10.6 for Details)					
Evaluation	**Screening**	**SUBOXONE Dosing[a]**	**Clinic Admission[a]**			**SUBLOCADE Injection**		
Day		**-14 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**
Informed Consent[b]	X							
Inclusion/Exclusion Criteria	X							
Demographics	X							
Medical/Psychiatric History	X							
Drug Use History	X							
Height/Weight/BMI[c]	X							
12-Lead ECG[d]	X		X					
Vital Signs[e]	X		X			X	X	X
Physical Examination[f]	X							
Adverse Event Assessment	<----------X---------->							
Concomitant Medications[g]	<----------X---------->							
Haematology	X							
Serum Chemistry	X							
HIV-1/HIV-2, Hep B, and Hep C Antibody Testing[h]	X							
Liver Function Testing[i]			X					X
PTT/PT/INR	X							
Urinalysis	X							
Urine Pregnancy Test[j]	X		X					
Urine Drug Screen (UDS)[k]	X							
SUBOXONE Administration		X	X[l]	X	X			

		Inpatient/ Outpatient	Inpatient (See Section 10.6 for Details)					
Evaluation	**Screening**	**SUBOXONE Dosing[a]**	**Clinic Admission[a]**			**SUBLOCADE Injection**		
Day		**-14 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3**
Randomisation Criteria Reviewed						X		
Randomisation						X		
PK Sampling[m]				X	X	X	X	X
SUBLOCADE Administration						X		
Injection Site Evaluation[n]						X		
Injection Site Grading[o]						X		
Injection Site Pain VAS[p]						X		
Discharge from Residential Facility								X
Psychosocial/Behavioural Counselling[q]		<----------X---------->						

BMI=body mass index; ECG=electrocardiogram; Hep=Hepatitis; HIV=human immunodeficiency virus; ICF=informed consent form; INR=international normalised ratio; PK=pharmacokinetic; PT=prothrombin time; QD=once daily; VAS=visual analogue scale; PTT=partial thromboplastin time

a. All participants must be administered 12 mg SUBOXONE QD as part of the study (after signing ICF) at least 7 days before SUBLOCADE injection. Participants may be administered SUBOXONE as part of the study (inpatient or outpatient) for a maximum of 14 days, with all participants completing the last 3 days as inpatients.
b. Informed consent form will be signed before screening procedures are initiated. Screening assessments must be completed within 30 days of SUBOXONE dosing for this study.
c. Body mass index will be calculated within the database using weight and height.
d. 12-lead ECGs will be collected after the participant has been in a supine position for ≥5 minutes and performed prior vital signs and to clinical laboratory tests (haematology, serum chemistry, and urinalysis).
e. Vital signs include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate after the participant has been in a supine or sitting position for ≥3 minutes. On Day 1, vital signs will be taken ≤60 minutes prior to SUBLOCADE administration and 1 and 8 hours post dose. Vital signs will also be taken on Day 2 at 24 hours and Day 3, 48 hours (see Section 10.6 [appendix] for assessment windows).
f. 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.
g. 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.
h. 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. If there is a positive result for HIV-2/HIV-2 or Hep C, an additional blood draw will be collected at the following site visit for confirmatory testing.

i. A subset of serum chemistry to be performed including alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, total protein, gamma glutamyl transferase, and lactate dehydrogenase only.
j. Required for female participants of childbearing potential only.
k. Qualitative test to be performed at Screening including the following: opioids (including fentanyl, oxycodone, opiates/morphine, and methadone), cocaine, amphetamines, cannabinoids, barbiturates, benzodiazepines, methamphetamine, phencyclidine.
l. 12 mg SUBOXONE QD should be administered at approximately at the same time each day. Therefore, on Day -3, the SUBOXONE administration may occur prior to clinic admission.
m. A 6-mL blood sample will be collected for PK analysis (see Section 10.6 [appendix] for assessment windows)
n. Injection site will be evaluated for signs of attempted removal. Any injection site reactions or infections will be recorded as AEs.
o. Injection site grading will be performed within 10 minutes after injection and again at 2 hours post injection (see Section 10.6 [appendix] for assessment windows).
p. Injection site pain will be assessed by the participant using a 100 mm VAS scale. The Injection Site Pain VAS scores will be obtained (after the completion of the injection) at 1, 5, 10, 15 and 30 minutes (see Section 10.6 [appendix] for assessment windows).
q. Psychosocial/behavioural counselling should be performed per standard of care as part of the SUBOXONE/SUBLOCADE treatment plan and should be documented into the source records.

Table 3 Schedule of Events – Outpatient Day 4 to End of Study

	Outpatient Period/Follow-Up									
Day	**4**	**6**	**8**	**11**	**15**	**18**	**22**	**25**	**29 (EOT/ET)**	**EOS[a]**
Visit Window	**NA**	**NA**	**NA**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±2**
AE Assessment	<----------X---------->									X
Concomitant Medications[b]	<----------X---------->									
PK Sampling[c]	X	X	X	X	X	X	X	X	X	
Vital Signs[d]									X	
Urine Drug Screen[e]									X	
Liver Function Test[f]									X	
Injection Site Evaluation			X		X				X	
Psychosocial/Behavioural Counselling	X	X	X	X	X	X	X	X	X	
Post-study Treatment Options[g]							X	X	X	

AE=adverse event; EOS=end of study; EOT=end of treatment; ET=early termination; PK=pharmacokinetic

a. Any participant with ongoing AEs at the EOT or ET visit will also be followed up by phone 2 weeks later for the EOS visit to assess any ongoing AEs and concomitant medications associated with those ongoing AEs only.
b. Includes a review of ongoing medications (including over-the-counter) and herbal supplements.
c. A 6-mL blood sample will be collected for PK analysis, as close to the time of SUBLOCADE injection performed on Day 1 as possible.
d. Vital signs include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate after the participant has been in a sitting or supine position for ≥3 minutes.
e. Qualitative test to be performed including the following: opioids (including fentanyl, oxycodone, opiates/morphine, methadone), cocaine, amphetamines, cannabinoids, barbiturates, benzodiazepines, methamphetamine, phencyclidine.
f. Blood sample to be collected for a subset of serum chemistry including alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, total protein, gamma glutamyl transferase, and lactate dehydrogenase only.
g. Alternative treatment options should be discussed with the participant for initiation after EOT, including the possibility of joining another Indivior study (eg, INDV-6000-406, Long-Term Outcomes).

2 INTRODUCTION

SUBLOCADE® (extended-release BUP injection) for SC use (CIII) contains BUP, a partial mu-opioid receptor agonist, and is indicated for the treatment of moderate to severe OUD.

2.1 Study Rationale

SUBLOCADE is currently approved for SC administration in 4 different quadrants of the abdomen. Injection locations are rotated to minimise irritation.

Having 1 or more alternate injection sites is desirable in this patient population who may be taking SUBLOCADE for extended durations, based upon clinical response.

Data cited from literature suggests that the proposed alternative injection locations for SC administration are viable options for delivering similar PK properties: back of upper arm, buttocks, and thigh.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of SUBLOCADE is provided in the prescribing information.

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

2.3 Benefit/Risk Assessment

BUP 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. SUBLOCADE has been shown to be an efficacious and safe treatment for moderate to severe OUD.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of SUBLOCADE may be found in the prescribing information.

2.3.1 Risk Assessment

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

The systemic safety profile for SUBLOCADE, given by a health care provider in clinical studies, is consistent with the known safety profile of TM BUP with the expected exception of injection site reactions.

A single injection of SUBLOCADE 300 mg provides BUP C_{max} and average plasma concentration corresponding to 12 mg/day of TM BUP and BUP plasma concentrations well below those measured for SUBLOCADE 300 mg at steady-state in the Phase III programme.

[redacted]

2.3.2 Benefit Assessment

SUBLOCADE is an approved product for treatment of OUD. Clear efficacy was demonstrated in the pivotal and additional supporting studies of the SUBLOCADE clinical development programme (detailed information provided in the applicable product prescribing information). The results of the primary and key secondary efficacy analyses from the Phase III double-blind study are compelling and are supported by results from other secondary endpoints.

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

In this study, participants will be initiated on TM BUP and will receive a single injection of SUBLOCADE 300 mg. Successful treatment outcomes are associated with retention and engagement in a treatment programme. It is important for participants to have access to continuing care at the conclusion of the study.

2.3.3 Overall Benefit Risk Conclusion

Taking into account the additional monitoring visits and other measures designed to minimise risk to participants in this study, the potential risks identified in association with SUBLOCADE are justified by the anticipated benefits that may be afforded to participants with OUD.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Objective	Corresponding Endpoint
Primary	
• To assess the relative bioavailability of BUP when administered at alternative injection locations (test treatments), in comparison to the abdomen (reference treatment) following a single SC injection of SUBLOCADE in participants with OUD	• $AUC_{0\text{-}28days}$ and C_{max} for BUP
Secondary	
• To evaluate the safety and tolerability of SUBLOCADE when administered at alternative injection locations, in comparison to the abdomen	• Proportion of participants with TEAEs • Proportion of participants with TEAEs identified as injection site reactions • Proportion of participants with treatment-emergent SAEs • Injection site grading at 10 minutes and 2 hours post SUBLOCADE dosing • Injection Site Pain VAS at 1, 5, 10, 15, and 30 minutes post SUBLOCADE dosing
Exploratory	
• To assess other BUP PK parameters • To assess the relative bioavailability of norbuprenorphine • To assess other norbuprenorphine PK parameters	• AUC_{last}, T_{max}, and C_{trough} for BUP • $AUC_{0\text{-}28days}$, AUC_{last}, and C_{max} for norbuprenorphine • T_{max} and C_{trough} for norbuprenorphine

AUC=area under the curve; BUP=buprenorphine; C_{max}=maximum plasma concentration; C_{trough}=trough plasma concentration measured on Day 29; OUD=opioid use disorder; SAE=serious adverse event; SC=subcutaneous; TEAE=treatment-emergent adverse event; T_{max}=time to maximum plasma concentration; VAS=visual analogue scale

The primary clinical question of interest is the following: Is the bioavailability of BUP when SUBLOCADE is administered in the back of upper arm, buttocks, and thigh similar to that when administered in the currently approved location, the abdomen?

The estimand for the primary endpoints is described by the following attributes:

- Estimand strategy: While on treatment strategy.
- Population: PK evaluable population (see Table 6).
- Endpoints: $AUC_{0\text{-}28\ days}$ and C_{max} of BUP.
- Treatment condition: Administration of SUBLOCADE to 1 of the randomised injection site locations.
- Remaining intercurrent events: There are no other intercurrent events anticipated at this time.
- Population-level summary: The ratio of geometric means and corresponding 90% CI for each alternative injection site vs the reference site (abdomen).

4 STUDY DESIGN

4.1 Overall Design

This is a multicentre, randomised, open-label, single-dose, parallel-group study in participants with moderate or severe OUD (based on criteria from the DSM-5 or documented history of moderate to severe OUD and receiving/stabilised on MOUD).

Participants will provide written informed consent before any protocol-related procedures commence within 30 days of the first SUBOXONE dose administered as part of this study (ie, after signing the ICF; see Section 10.1 [appendix] for details). The study includes both a Residential (Inpatient) Period and a Non-Residential (Outpatient) Period.

Following Screening, all eligible participants must be stabilised on 12 mg SUBOXONE (BUP/naloxone) sublingual film QD for a minimum of 7 days before the SUBLOCADE injection. Dose induction/stabilisation onto SUBOXONE may be completed as outpatient or inpatient, as necessary, according to the prescribing information for a maximum of 14 days before SUBLOCADE injection.

All participants will be admitted to the residential facility by the evening of Day -3.

The period from the first dose of SUBOXONE administered as part of this study through Day -1 will be referred to as the Run-in Period.

Following the Run-in Period, on Day 1, eligible participants will be randomised to a treatment arm.

Each treatment arm will receive a single, SC injection of 300 mg SUBLOCADE at a different injection location ie, abdomen (reference) or one of the alternative injection locations (test) ie, back of upper arm, buttocks, and thigh.

Safety measurements and blood samples for PK assessments during the Residential Period will be collected at scheduled time points until the participants are discharged from the residential facility on Day 3.

Participants will return to the clinical facility as outpatients for safety and PK assessments to be conducted according to the SoE until EOT. Alternative treatment options should be discussed with the participant for initiation after EOT, including the possibility of joining another Indivior study (eg, INDV-6000-406).

Any participant with ongoing AEs at the EOT or ET visit will also be followed up by phone 2 weeks later for the EOS visit to assess any ongoing AEs and concomitant medications associated with those ongoing AEs only.

It is important that participants do not use any BUP-containing products, either therapeutically or illicitly. Such use would compromise the PK assessment of BUP and its metabolite, norbuprenorphine.

Approximately 80 participants in the United States will be randomised in total, ideally to achieve 15 completed participants per each of the 4 treatment arms (injection locations): abdomen (reference), back of upper arm, buttocks, and thigh. The total duration of the study for each participant, including Screening (up to 30 days), Run-in (up to 14 days), Treatment (28 days), and possible Follow up (2 weeks), will be up to approximately 86 days.

Participants who prematurely discontinue from the study will not be replaced.

4.2 Scientific Rationale for Study Design

While having 1 or more alternate injection location is desirable in this patient population, it needs to be demonstrated that there is similar bioavailability of BUP when SUBLOCADE is injected in different locations. In addition, it needs to be assessed whether the injections are safe and tolerable (eg, with respect to injection site pain) at the different injection locations. The primary and secondary objectives and endpoints are aligned with these requirements.

It is anticipated that measuring the PK profile at the times outlined in Section 10.6 (appendix) will provide adequate data to compare the bioavailability of BUP after SUBLOCADE injection between the alternate injection locations and the abdomen (reference location). Likewise, the collection of TEAEs and injection location information (grading and VAS) will provide a safety and tolerability profile that can be compared between alternate injection locations vs the abdomen.

All of these assessments have been used in previous studies by Indivior, including in those that provided adequate and well-controlled data to support the marketing application.

4.3 Justification for Dose

The dose selected for this study reflects the prescribing information for the first SUBLOCADE injection and is the highest dose strength approved.

4.4 End of Study Definition

The end of the study is defined as the date on which the last participant completes the last assessment to collect final data for the primary outcome measures, secondary outcome measures, and adverse events (that is, the last participant’s last visit).

A participant is considered to have completed the study if the participant has completed the last scheduled procedure shown in the SoE (Section 1.3).

4.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or ICH/GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study-site staff. It is the responsibility of the investigator and study-site staff to use continuous vigilance to identify and report deviations to Indivior or specified designee, and to the IRB/IEC per local requirements.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Signed the ICF and have the ability to comply with the requirements and restrictions listed therein.
2. Sex: male or female.
3. Between the ages of 18 and 65 years inclusive, at the time of signing the ICF.
4. Currently meets DSM-5 criteria for moderate or severe OUD, or documented history of moderate to severe OUD and receiving/stabilised on MOUD.
5. Body mass index: ≥18.0 to ≤33.0 kg/m^2.
6. New to treatment and seeking MOUD, or currently prescribed TM BUP for OUD at the dose of 12 mg daily or can dose adjust to 12 mg daily .
7. Agree not to take any BUP-containing products, other than those administered for the current study, throughout the duration of the study.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has current diagnosis, other than OUD, requiring chronic opioid treatment.
2. Has concurrent primary substance use disorder, as defined by DSM-5 criteria, other than opioid, tobacco, cannabis, or mild to moderate alcohol use disorders.
3. Has target areas unsuitable for SC injections or evaluation of injections site (eg, nodules, scarring, lesions, excessive pigment) in the areas designated for possible injection in the study.
4. Has had significant traumatic injury or major surgical procedure (as defined by the investigator) within 30 days prior to the first dose of SUBLOCADE or still recovering from prior such injury or surgery.
5. Known personal and/or family history of congenital QT prolongation, or taking Class IA antiarrhythmic medications (eg, quinidine, procainamide, disopyramide) or Class III

antiarrhythmic medications (eg, sotalol, amiodarone) or other mediations that prolong the QT interval. Known family history of sudden unexplained death.

6. Currently taking (within the 30 days prior to signing the ICF) prescription or over-the-counter medications that are clinically relevant CYP 3A4 or CYP 2C8 inducers or inhibitors (eg, rifampin, azole antifungals [eg, ketoconazole], macrolide antibiotics [eg, erythromycin]). See Section 10.5 (appendix) for a list containing examples of excluded medications.
7. Has history of suicidal ideation within 30 days prior to informed consent or history of a suicide attempt in the 6 months prior to informed consent.
8. Has any active medical condition, or psychiatric illness, or social/legal situation (including court order requiring treatment for OUD), or organ disease, or concurrent medication/treatment that may compromise participant safety, interfere with study endpoints, or limit compliance with study requirements, or compromise the ability of the participant to provide written informed consent.
9. Moderate or severe hepatic impairment (Child-Pugh B or C).
10. Has known allergy or hypersensitivity to BUP or any component of the ATRIGEL Delivery System.
11. Concurrent or has had prior treatment with any BUP long-acting injectable product (eg, SUBLOCADE) in the past 3 years prior to consent; or treatment with depot naltrexone within the 3 months prior to consent.
12. Treatment with another investigational agent within 30 days prior to Screening or enrolment in another clinical study (except for an observational study).
13. Concurrent treatment with medications contraindicated for use with BUP as per local prescribing information.
14. Is a member of site staff, has a financial interest in Indivior, or is an immediate family member of anyone directly involved in the study (ie, site staff or Indivior employee).

5.3 Randomisation Criteria

1. Females of reproductive potential must have a negative urine pregnancy test on Day -3.
2. Dose-stabilised on 12 mg QD of SUBOXONE sublingual film for a minimum of 7 days (last dose on the morning of Day -1).

5.4 Lifestyle Considerations

5.4.1 Concomitant Medications

Eligible participants that are new to treatment with BUP 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 at least 24 hours before SUBOXONE induction. Participants will be informed that under reporting their last use of opioids and undergoing induction with remaining exposure to opioids places them at high risk for rapid and intense onset of withdrawal symptoms. Risk is increased with

high doses of potent opioids, such as fentanyl; an on-site dipstick UDS at Screening to identify current opioids of abuse will support this discussion between investigator and trial participant.

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

5.4.2 Activity

Participants should avoid strenuous exercise from Day -1 until Day 3 after SUBLOCADE dosing.

5.4.3 Other Restrictions

Participants may be restricted for smoking and use of nicotine-containing products during their time in the inpatient research clinic, per local site restrictions.

Participants will be asked to refrain from donating blood for the duration of their study participation.

5.5 Screen Failures

See Table 6 for the definition of an enroled participant.

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently given study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, reason for screen failure, such as not eligible, withdrew consent, AE), eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened with documented approval from the medical monitor. Rescreened participants should be assigned a new participant number.

5.6 Criteria for Temporarily Delaying Administration of Study Intervention

Participants may be administered SUBOXONE as part of this study for more than 14 days before the SUBLOCADE injection only with documented approval from the medical monitor.

Delays of enrolment are not permitted, screening assessments must be completed within 30 days prior to the first dose of study drug.

5.7 Run-in Failure

A participant will be considered a run-in failure if the participant doses with SUBOXONE as part of this study and is not administered with SUBLOCADE.

5.8 Early Discontinuation

A participant will be considered an early discontinuer if the participant received study drug and did not complete all visits. Reasons for not completing all visits will be captured in the participant source documents and the eCRF.

The definition of a study completer is provided in Section 4.4.

6 STUDY DRUG AND CONCOMITANT THERAPY

Study interventions (ie, study drugs and concomitant medications) are all pre-specified, investigational and non-investigational medicinal products, medical devices, and other interventions (eg, surgical and behavioural) intended to be administered to the study participants during the study conduct.

Study drug is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. Medicinal products with a marketing authorisation are study drugs when they are to be used as the test substance, reference substance, or comparator in a clinical study, provided the requirement(s) in the definition is/are met.

Concomitant medication is a medicinal product that is not classified as study drug, but may be taken by participants during the study, eg, concomitant or rescue/escape medication used for preventative, diagnostic, or therapeutic reasons or medication given to ensure that adequate medical care is provided for the participant during a study.

6.1 Study Drugs Administered

The following table presents study drugs to be administered in this protocol.

Table 5 Study Drugs Administered – Label

Drug Name	SUBLOCADE® (BUP)	SUBOXONE® (BUP/naloxone)
Study Drug Description	Single SC injection, 300 mg	Sublingual film 12 mg once daily for a minimum of 7 days prior to SUBLOCADE injection
Type	Drug	Drug
Dose Formulation	Extended-release injection	Sublingual film
Unit Dose Strengths	300 mg/1.5 mL provided in a prefilled syringe	2, 4, and 12 mg
Dosage Levels	300 mg	12 mg once daily for a minimum of 7 days prior to SUBLOCADE injection
Duration of Administration	Single dose	Minimum of 7 days prior to SUBLOCADE injection
Route of Administration	SC injection	Sublingual
Use	Experimental	Experimental
Study Drug and Concomitant Medication	Study drug	Study drug
Sourcing	[redacted]	
Packaging and Labelling		

BUP=buprenorphine; SC=subcutaneous

[redacted]

6.2 Preparation, Handling, Storage, and Accountability

[redacted]

6.2.1 Drug Preparation

SUBLOCADE and SUBOXONE will be prepared according to the Instructions for Use in the applicable product labelling information.

6.2.2 Drug Administration

Time of dose for SUBLOCADE is defined as the time the SC injection is complete. The time of dose and any dosing observations (eg, 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.

Time of dose for SUBOXONE is defined as the time the TM BUP is placed into the oral cavity. Participants should be administered 12 mg SUBOXONE QD at approximately the same time each day.

All unused study drug will either be destroyed by the investigator, as per local SOPs, or returned to the clinical study drug distributor, as agreed with the sponsor. The study drug must be handled strictly in accordance with the protocol, Pharmacy Manual, Safety Data Sheet, and the local prescribing information; it must be stored in a locked, limited access area under appropriate environmental conditions.

All study drug dispensation will be performed by a pharmacist or designee, checked by a study-site staff member and documented on a drug dispensation form. Unused study drug must be available for verification by the site monitor during on-site monitoring visits.

6.2.3 Reporting Product Complaints

The investigator and study-site staff are responsible for prompt recognition and reporting of product quality complaints to Indivior.

A product complaint is any concern pertaining to the manufacturing or quality control of the study drug and includes, but is not limited to, 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.

See the pharmacy manual for further details.

6.3 Assignment to Study Intervention

The investigator is responsible for maintaining a master list (ie, a participant identification list) of all consented participants and will document all participants that did not meet study eligibility criteria (ie, screen failures), including reason(s) for ineligibility (ie, a participant screening and enrolment log).

All participants will receive the same study drugs, however, will be centrally assigned to a randomised injection location using an IWRS. Before the study is initiated, the directions for the IWRS will be provided to each site.

6.4 Blinding

This is an open-label study; however, the randomisation number will be assigned via the IWRS, using central, blocked, stratified randomisation schedules. The randomisation factor will be SUBLOCADE injection location. The site will contact the IWRS prior to the start of study drug administration for each participant. The site will record the injection location assignment on the applicable CRF, if required.

6.5 Study Drug Compliance

All participants are dosed with SUBLOCADE at the site, so they will receive study drug directly from the investigator or designee, under medical supervision. The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

The site personnel administering the dose will examine the injection site at each visit for evidence of tampering.

Any doses of SUBOXONE administered at the site, dispensed to the participant, and taken by the participant outside of the clinic should be recorded. For reconciliation and study drug compliance, participants will be asked to return any study drug not taken as well as all empty

packaging for all study drug taken. The investigator may ask the participant to return for dose adjustment as many times as necessary during induction and stabilisation.

6.6 Dose Modification

During the Run-in Period, SUBOXONE doses will be adjusted over time to achieve the target 12 mg dose once daily.

Modification of the SUBLOCADE dose is not permitted.

6.6.1 Retreatment Criteria

Not applicable

6.7 Treatment Access to Study Drug After the End of the Study

SUBLOCADE is an approved MOUD. Alternative treatment options should be discussed with the participant for initiation after EOT, including the possibility of joining another Indivior study (eg, INDV-6000-406, Long-Term Outcomes).

6.8 Treatment of Study Drug Overdose

For this study, any dose of TM BUP greater than 24 mg daily, or more than 1 injection of SUBLOCADE during this study will be considered an overdose.

The antidote to study drug is Naloxone and may be used in case of symptomatic overdose with respiratory depression.

In the event of a study drug overdose, the investigator/treating physician should do the following:

1. Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study drug should be interrupted or the injection depot should be removed.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow up.
3. Obtain a plasma sample for PK analysis if requested by the medical monitor (requirement and time frame from last dose will be determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose.

Any instance of study drug overdose must be communicated within 24 hours and fully documented (see Section 8.4). Details of any signs or symptoms and their management should be recorded, including details of any antidote(s) administered.

6.9 Prior and Concomitant Therapy

Any prior prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) taken within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of dosing with SUBOXONE for this study should be recorded in the source documents and in the eCRF.

The investigator may prescribe concomitant medications or treatments deemed necessary to the participant, with the exception of those medications defined in Section 6.9.1 and Section 6.9.2.

Concomitant medication uses will be collected from Screening through the completion of the EOT visit at the time points listed in Section 1.3. 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.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Prohibited Concomitant Therapies

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

Participants are not permitted to take any more than 12 mg of SUBOXONE during the 7 days of dose stabilisation, nor supplemental TM BUP after the SUBLOCADE injection.

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

Other concomitant therapies (inhibitors/inducers of cytochrome P450 3A4 or 2C8) subject to the restrictions indicated in Section 10.5 (appendix) may be used only following approval by the sponsor unless a medical need necessitates their use.

6.9.2 Restricted Concomitant Therapies

Due to additive pharmacologic effects, the concomitant use of benzodiazepines or other central nervous system depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death. However, a 2017 FDA Drug Safety Communication noted that although concomitant use of BUP or methadone with benzodiazepines increases the risk of an adverse reaction, including overdose death, opioid agonist treatment should not be denied to patients solely on the basis of their taking benzodiazepines, because untreated OUD can pose a greater risk of morbidity and mortality. The FDA advises that careful medication management by health care professionals can reduce risk (see https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-urges-caution-about-withholding-opioid-addiction-medications for more information).

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

- Benzodiazepines and other central nervous system depressants
- Antiretrovirals: non-nucleoside reverse transcriptase inhibitors
- Antiretrovirals: protease inhibitors

- Serotonergic drugs
- Monoamine oxidase inhibitors
- Muscle relaxants
- Diuretics
- Anticholinergic drugs

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

6.9.3 Permitted Concomitant Therapies and Rescue Medication

The investigator may prescribe concomitant medications or treatments deemed necessary to the participant, except those medications defined in Section 6.9.1 and Section 6.9.2 of this protocol.

If the participant experiences withdrawal symptoms at any time, he/she may be treated symptomatically. Below are the concomitant therapies listed in SAMHSA TIP 63 2020:

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

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

7 DISCONTINUATION OF STUDY DRUG, PARTICIPANT DISCONTINUATION/WITHDRAWAL AND STOPPING CRITERIA

7.1 Discontinuation of Study Drug and Study Stopping Criteria

Not applicable for this single-dose study.

7.2 Participant Discontinuation/Withdrawal From the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (with or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoE (Section 1.3). See SoE for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study drug and from the study at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3 Lost to Follow Up

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

An enroled participant who has received study drug will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee should make every effort to regain contact with the participant (where possible, 2 contact attempts (eg, telephone calls and/or emails). A certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- For the purpose of documenting date of discontinuation for a participant confirmed to be lost to follow-up, the date of discontinuation should be the date of last contact with the participant.
- In the case where a certified letter is sent but not confirmed as received by the participant, the date of discontinuation is the date the certified letter was sent.
- In the case where a certified letter is sent and has been confirmed as received by the participant, the date of discontinuation is the date of the confirmed participant receipt.
- In the event that neither of these above cases applies (which should be explained in the source documents), the date of discontinuation is the date of the participant's last study visit.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Administrative and General Procedures

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

Any relevant medical and psychiatric history will be obtained during the Screening Period. This will include information regarding the participant's history of medical and psychiatric conditions, diagnoses, procedures, treatments, medications, demographics (including sex, race, age, and ethnicity).

A detailed history of drug use and drugs of abuse (illicit and prescribed) will capture the drug class, compounds, routes, dose, and frequency of use for lifetime and for the past 30 days.

Eligible participants must have documented history of moderate or severe OUD as defined by DSM-5 criteria and must be seeking medication for treatment of OUD. Any updates to medical or psychiatric history information made available during the study will be captured.

8.2 Efficacy Assessments

Efficacy is not evaluated in this study.

8.3 Safety Assessments

Safety will be measured using the following assessments:

- TEAEs including the following:
  - TEAEs identified as injection site reactions
  - SAEs
  - TEAEs leading to treatment discontinuation
- Injection site grading
- Injection Site Pain VAS

Planned time points for all safety assessments are provided in the SoE.

8.3.1 Physical Examinations

A complete physical examination will be conducted by the investigator or a medically qualified sub-investigator according to the SoE (Section 1.3). 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).

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

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Local Injection Site Tolerability

8.3.2.1 Injection Site Grading

Local injection site grading will be performed by the investigator or a trained and certified health care professional, according to the SoE in Section 1.3 and Section 10.6 (appendix). Injection sites will be assessed for pain, tenderness, erythema/redness, induration, or swelling. Local injection site tolerability will be assigned a severity grade, including none (grade 0), mild (grade 1), moderate (grade 2), severe (grade 3), or potentially life-threatening (grade 4) utilising the Injection Site Grading Scale.

8.3.2.2 Injection Site Evaluation

The SUBLOCADE injection site will be evaluated according to the SoE in Section 1.31.3 and Section 10.6 (appendix). Any signs of attempted depot removal must be discussed with the medical monitor to determine if the participant should remain in the study. Any injection site reactions or infections will be recorded as AEs.

8.3.2.3 Injection Site Pain VAS

Injection site pain will be assessed by the participant at each injection visit on paper with a 100 mm VAS scale, where 0 represents no pain and 10 represents maximum pain according to the SoE in Section 1.3 and Section 10.6 (appendix). The timing of the Injection Site Pain VAS should be measured from the end of the injection. In addition to rating pain levels by marking on the line the point they feel best represents their perception of their current state, the participant will also answer the following question with either a Yes or No: Are you currently experiencing any burning or stinging at the injection site?

8.3.3 Vital Signs

Vital signs will be measured in a sitting or supine position after 3 minutes rest according to the SoE in Section 1.3 and Section 10.6 (appendix). These assessments will include temperature, systolic, and diastolic blood pressure, and pulse and respiratory rate.

8.3.4 Clinical Safety Laboratory Tests

See Section 10.2 (appendix) for the list of clinical laboratory tests to be performed and to the SoE (Section 1.3) for the timing and frequency.

The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.

All protocol-required laboratory tests, as defined in Section 10.2 (appendix), must be conducted in accordance with the laboratory manual and the SoE.

If laboratory values from non–protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.3.5 Electrocardiograms

12-Lead ECGs will be performed as indicated in the SoE, Section 1.3. All ECGs will be performed after the participant has been in the supine position for a minimum of 5 minutes. Recordings will be taken using an ECG machine that automatically calculates the heart rate as well as measures PR, QRS, QT, and QTcF intervals.

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

8.3.6 Pregnancy Testing

During the study, pregnancy urine testing will be performed per the SoE, Section 1.3 to confirm that the participant is not pregnant before dosing. For further details regarding pregnancy reporting, refer to Section 8.4.5.

8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs are provided below, as are criteria for assessment of AE/SAE intensity and causality.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. Any clinically significant symptoms will be reported as AEs. All AEs and corresponding treatment will be recorded in the eCRFs and a summary of all safety data will be presented in the final CSR. Any ongoing AEs will be appropriately followed up until resolution or 14 days after EOT/ET (defined as the EOS visit).

AE Definition

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline (signing of the ICF), considered clinically significant in the medical and scientific judgement of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug administration even though it may have been present before signing the ICF.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction or that resulted in additional intervention (eg, concomitant medication, surgery).
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose should be reported as an AE unless serious criteria are met, including an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported in 24 hours regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events Not Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- Any abnormal laboratory findings or other abnormal safety findings that are not considered to be clinically significant by the investigator.
- The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (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 at or detected after signing the ICF that do not worsen.

Definition of SAE

An SAE is defined as any untoward medical occurrence that:

a. Results in death
b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

- In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or 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.
- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline (signing of the ICF) is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of study drug dependency or study drug abuse.

Any instance of overdose (whether or not it involved study drug) must be communicated within 24 hours and fully documented. Details of any signs or symptoms and their management should be recorded, including details of any antidote(s) administered.

An SAE must be reported for participants with ALT or AST ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct).

Definition of SUSAR

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

applicable product labelling information and will notify the IRB/EC, if required according to local requirements.

Assessment of Intensity

The investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Indivior Pharmacovigilance. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Indivior Pharmacovigilance.
- The investigator may change opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Clinical Laboratory Changes

Changes in laboratory values, vital signs, or other safety parameters (eg, neurological and clinical symptom assessments) as noted in the protocol are a subset of AEs and are reportable only if the laboratory test result is considered to be clinically significant by the investigator or medically qualified designee. Generally, these findings would be associated with accompanying symptoms, and/or require additional diagnostic testing or intervention (medical, surgical),

and/or require additional significant treatment, and/or require temporal or permanent discontinuation of study drug..

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

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoE (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from first becoming aware of the event, as indicated in Section 8.4.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor.

Additional PK samples may be collected for participants who experience an SAE. Samples should be collected as soon as the investigator is made aware of the SAE and additional blood samples may be collected, after a period of time, to confirm resolution of the SAE.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Reporting and Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, the event is otherwise explained or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 8.4.3.2.

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 using the form provided by Indivior or designated representative. 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 8.4.

8.4.3.1 Reporting of SAEs

SAE Reporting to Indivior

- The primary mechanism for reporting an SAE, or an update to an existing SAE, to Indivior Pharmacovigilance will be by completing a paper SAE Reporting Form and submitting via email or Facsimile transmission:

  [redacted]

  Indivior
  10710 Midlothian Turnpike, Suite 125
  North Chesterfield, VA 23235
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE Reporting Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

8.4.3.2 Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Indivior in lieu of completion of the SAE Reporting Form.
- There may be instances when copies of medical records for certain cases are requested by Indivior Pharmacovigilance. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Indivior Pharmacovigilance.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Indivior Pharmacovigilance to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide Indivior Pharmacovigilance with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IEC, and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

Female participants who become pregnant

- If a female participant suspects that she is pregnant (eg, missed period, self-administered pregnancy test) during treatment or within 3 months of the last dose of SUBOXONE (for participants who receive only SUBOXONE) and until 12 months following the dose of SUBLOCADE (approximately 6 to 8 terminal half-lives) after the discontinuation of study drug, treatment will be stopped immediately, where applicable. The participant will be instructed to return to the clinical unit as soon as possible (preferably within 48 hours) or at the next visit to undergo a serum pregnancy test.
- In the case where a participant's routine pregnancy test as required per protocol is positive for pregnancy, treatment will be stopped immediately. If the participant has a positive urine pregnancy test, a confirmatory serum pregnancy test should be performed. The investigator should fully inform the female participant of the serious risk to the fetus as well as discuss the desirability of continuing the pregnancy.
- Pregnancy of a study participant without associated unexpected or adverse sequelae is not a reportable AE but must be reported to Indivior Global Safety (or designated representative) using the Safety Information Collection Form within 24 hours of the Investigator or designee first being aware of the pregnancy (contact details for reporting via email or fax are the same as for SAEs).
- Abnormal pregnancy outcomes (eg, fetal death, stillbirth, congenital anomalies, ectopic pregnancy, abortion [except pregnancy in habitual aborter, prophylaxis of abortion], pre-eclampsia, eclampsia) are considered SAEs and will be reported as such.

- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. 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 fetal status (presence or absence of anomalies) or indication for procedure.
- Any poststudy pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former participant, he or she may learn of an SAE through spontaneous reporting.

8.5 Pharmacokinetics

- Blood samples of approximately 6 mL will be collected for measurement of plasma concentrations of BUP and norbuprenorphine at times points specified in the SoE.
- Additional samples may be collected for participants who experience an SAE. Samples should be collected as soon as the investigator is made aware of the SAE and additional blood samples may be collected, after a period of time, to confirm resolution of the SAE.
- Instructions for the collection and handling of samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Briefly, blood will be collected in a pre-labelled 6-mL K_2EDTA vacutainer tube by individual venipuncture. Blood samples will be centrifuged and the plasma will be transferred into 2 aliquots of approximately 1.5 mL each in pre-labelled polypropylene tubes. Plasma samples will be stored at -20°C until analysis.
- The plasma concentration of BUP and norbuprenorphine will be quantified using a previously validated liquid chromatography tandem mass spectroscopy method.

8.6 Pharmacodynamics

Not applicable

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Health Economics

Health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

No formal statistical hypotheses will be tested in this study. Relative bioavailability of BUP when administered to alternative injection sites (back of upper arm, buttocks, and thigh) compared to that when administered to the abdomen will be informally evaluated.

9.1.1 Multiplicity Adjustment

Not applicable for this study.

9.2 Analyses Sets

For purposes of analysis, the following populations are defined:

Table 6 Populations for Analysis

Population	Description
Screened	All participants who sign the ICF.
Enroled	All screened participants who received the first dose of SUBOXONE film during run-in.
Randomised	All enroled participants who are randomised to one of the 4 treatment arms (injection locations).
PK Analysis Set	All randomised participants who receive SUBLOCADE injection and provide at least 1 PK sample post randomisation. The participants will be analysed corresponding to the injection location used.
PK Evaluable Analysis Set	All randomised participants who receive SUBLOCADE injection and provide an adequate number of post randomisation PK samples to derive key PK parameters for SUBLOCADE (ie, C_{max}, and $AUC_{0\text{-}28days}$). The participants will be analysed corresponding to the injection location used.
Safety Analysis Set	All enroled participants who received SUBLOCADE injection. The participants will be analysed corresponding to the injection location used.
Run-In Safety Analysis Set	All enroled participants who receive at least 1 dose of SUBOXONE film during run-in.

9.3 Statistical Analyses

9.3.1 General Considerations

Continuous variables will be summarised using descriptive statistics such as mean, SD, median, interquartile range, minimum, and maximum. Categorical variables will be reported as frequency counts (including number missing) and the percentage of participants in corresponding categories.

BUP and norbuprenorphine plasma concentrations following SUBLOCADE injection will be summarised at each scheduled time point by injection location using the PK Analysis set. BUP and norbuprenorphine plasma concentrations during run-in with SUBOXONE film will also be summarised at each scheduled time point using the Enroled participant set for participants who have at least 1 PK sample post SUBOXONE dose. Concentrations that are below the lower limit of quantification (BLQ) will be treated as zero for the summary statistics. Mean BUP and norbuprenorphine plasma concentration-time curves will be presented for the Run-in Period with SUBOXONE film for overall and for SUBLOCADE phase stratified by injection locations.

Details for handling missing and aberrant plasma concentrations for deriving BUP and norbuprenorphine PK parameters will be detailed in the SAP.

9.3.2 Primary Analysis

9.3.2.1 Definition of Endpoints

The primary PK parameters of BUP following SUBLOCADE injection will be derived as shown in Table 7 using the PK evaluable set. Calculations will be done by noncompartmental analysis using WinNonlin Phoenix version 6.3 or higher.

Table 7 Primary PK Parameters of BUP following SUBLOCADE injection

$AUC_{0\text{-}28days}$	Area under the concentration-time curve from study Day 1 to Day 29 of BUP, calculated by the linear trapezoidal method
C_{max}	Maximum observed plasma concentration of BUP

9.3.2.2 Main Analytical Approach

Natural log-transformed $AUC_{0\text{-}28days}$ and C_{max} from SUBLOCADE Phase for BUP will be analysed using an ANOVA model with injection site location as the independent variable. The 90% CI will be estimated for the ratio of population geometric means (test/reference) corresponding to exponentiated differences in least square means.

The comparisons of interest are the 3 alternative injection sites (test) versus abdomen (reference, namely: back of upper arm vs abdomen, buttocks vs abdomen, and thigh vs abdomen.)

9.3.3 Secondary Endpoint Analysis

All secondary endpoints summaries will be based on the Safety Population.

The following secondary endpoints will be derived as the proportion of participants reporting at least one of the specified events, and summarised using frequency counts and percentages:

- Proportion of participants with TEAEs
- Proportion of participants with TEAEs identified as injection site reactions
- Proportion of participants with treatment-emergent SAEs

TEAEs identified as injection site reactions will be summarised using customised MedDRA queries. Details of the customised MedDRA queries will be provided in the SAP.

Each component of the Injection site grading (induration, swelling, pain, tenderness and erythema) at 10 minutes and 2 hours post SUBLOCADE dosing will be summarised using frequency counts and percentages of participants reporting the specific level of severity.

Injection Site Pain VAS at 1, 5, 10, 15, and 30 minutes post SUBLOCADE dosing will be summarised using descriptive statistics.

All summaries will be by the injection site anatomical location and overall. No hypotheses testing will be performed to compare the injection site locations.

9.3.4 Exploratory Endpoint Analyses

The following PK parameters for SUBLOCADE will be derived as shown in Table 8 for BUP and Table 9 for norbuprenorphine using the PK Evaluable Analysis Set. Calculations will be done by noncompartmental analysis using WinNonlin Phoenix. The plasma terminal half-life and AUC extrapolated to infinity ($AUC_{0\text{-}inf}$) are not calculated as the duration of the PK evaluation is shorter than the half-life reported for SUBLOCADE (43-60 days).

Table 8 Additional PK Parameters of BUP Following SUBLOCADE Injection

AUC_{last}	Area under the concentration-time curve from time 0 to the last quantifiable BUP concentration, calculated by the linear trapezoidal method
T_{max}	Time to attain the maximum observed BUP plasma concentration
C_{trough}	Trough BUP plasma concentration measured on Day 29

Table 9 PK Parameters of Norbuprenorphine Following SUBLOCADE Injection

$AUC_{0\text{-}28days}$	Area under the concentration-time curve from Study Day 1 to Day 29 of norbuprenorphine, calculated by the linear trapezoidal method
AUC_{last}	Area under the concentration-time curve from time 0 to the last quantifiable concentration of norbuprenorphine, calculated by the linear trapezoidal method
C_{max}	Maximum observed norbuprenorphine plasma concentration
T_{max}	Time to attain the maximum observed norbuprenorphine plasma concentration
C_{trough}	Trough norbuprenorphine plasma concentration measured on Day 29

AUC_{last} for both analytes, and $AUC_{0\text{-}28days}$ and C_{max} for norbuprenorphine will be analysed using the same statistical ANOVA model as described in Section 9.3.2.

9.3.5 Other Safety Analyses

TEAEs are defined as AEs with a start time that is equal to or later than the initiation of the drug treatment or any AE already present that worsens in either severity or frequency following drug exposure. Specifically, TEAEs following exposure to SUBOXONE treatment will be associated with the Run-in Period and those following SUBLOCADE treatment will be associated with the Post-randomisation Period.

TEAEs will be summarised separately for the Post-randomisation Period and the Run-in Period using safety analysis set and run-in safety analysis set, respectively. The summaries will be by injection site and overall for the Post-randomisation Period, and overall only for the Run-in Period. Complete details of the safety analyses will be provided in the SAP.

Adverse events will be coded using MedDRA and grouped by system organ class. Incidence and incidence proportion of TEAE (number and percentage of participants reporting the TEAE at least once during the Post-randomisation Period and the Run-in Period, as applicable) will be summarised by system organ class and preferred term. Separate summaries will be provided for all TEAEs, TEAEs identified as injection site reactions, serious TEAEs, drug related TEAEs, and TEAEs leading to discontinuation of study treatment.

9.4 Interim Analysis

No interim analysis is planned.

9.5 Sample Size Determination

No formal statistical power analysis was performed to determine the sample size of this study. Based on historical experience from previous similar clinical trials, approximately 80 randomised participants was considered adequate to achieve at least 15 PK evaluable

participants per injection site location to assess the relative bioavailability of SUBLOCADE 300 mg at each of the alternate injection site locations compared to the abdomen (the reference injection location).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before use in the study. If required by local regulations, the protocol should be re-approved by the IRB/IEC annually. The IRB/IEC must be constituted and operate in accordance with the principles and requirements of ICH/GCP.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol may require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study to the participant and answer all questions regarding the study. Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and privacy and data protection requirements, where applicable, and the IRB/IEC or study centre.
- Written informed consent must be obtained prior to any study-related procedures.
- The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study, if required by the IRB/IEC.
- A copy of the ICF(s) must be provided to the participant.
- Any changes to the ICF must be reviewed and approved by Indivior before submission to the IRB/IEC.
- In the event that new safety information emerges that represents a significant change in the risk/benefit assessment, the ICF will be updated accordingly and submitted to the IRB/IEC for approval.

Participants who are rescreened are required to sign a new ICF.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- Participants must be informed that their study records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by the IRB/IEC, and by inspectors from regulatory authorities.
- All participant bodily fluids and/or other materials collected shall be used solely in accordance with the study protocol and the ICF signed by the participant, unless the participant agrees to additional procedures in writing with the sponsor.
- 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 (eg, for an IRB/IEC, Indivior, or regulatory inspection) along with the facility, study personnel, and supporting systems/hardware. All documents pertaining to the study, including all versions of the approved study protocol, copy of the ICF and other documents as required per local laws and regulations (eg, Health Insurance Portability and Accountability Act documents), completed CRFs, source records (participant records,

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

Where permitted by local laws and regulations, records may be maintained in a format other than hard copy (eg, 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 backup of any reproductions.

The minimum retention time for retaining study records will be in accordance with the strictest standard applicable for the study site as determined by local laws, regulations, or institutional requirements. At a minimum, records will be maintained as dictated by ICH/GCP guidelines, as well as in accordance with the site's SOP requirements. If the investigator withdraws from the study (eg, 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.

- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organisational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorised disclosure or access.

10.1.5 Committees Structure

Not applicable

10.1.5.1 Dissemination of Clinical Study Data

This study will be registered on ClinicalTrials.gov. Release of applicable clinical study results will proceed in compliance with local regulations in accordance with the principles of Good Publication Practice.

A CSR 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.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the data entry guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Investigator Site Audits include, but are not limited to, review of drug supply, presence of required documents, the informed consent process, comparison of CRFs with source documents, and any other study-specific information/documentation that the auditor deems appropriate for review during the audit. 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 CRO's Quality Assurance SOPs.
- In addition, this study is subject to inspections by regulatory authorities. If such a regulatory inspection occurs, the investigator agrees to allow the regulatory inspector direct access to all relevant study documents. The investigator must contact Indivior immediately if this occurs and must fully cooperate with the inspection conducted at a reasonable time in a reasonable manner.
- Monitoring details describing strategy including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organisations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as dictated by ICH/GCP guidelines, as well as in accordance with the site's SOP requirements and local regulations or institutional policies. No records may be destroyed without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- The investigator is responsible for the quality of the data recorded in the CRFs. The data recorded should be a complete and accurate account of the participant's record collected during the study.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents may be electronic, hard copy, or a combination of both and are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to

this study will be maintained by the investigator and made available for direct inspection by the authorised study personnel outlined in the ICF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8 Study and Site Start and Closure

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to the following:

For study termination:

- Discontinuation of further study drug development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Should this be necessary, Indivior, or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the investigator will inform the IRB/IEC of the same. In terminating the study, Indivior and the investigator will assure that adequate consideration is given to the protection of the participants' interests.

10.1.9 Publication Policy

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.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10 Protocol-required Safety Laboratory Tests

Laboratory Assessments	**Parameters**	
Haematology	Platelet count	
	Red blood cell (RBC) count	
	RBC indices: • Mean corpuscular volume (MCV) • Mean corpuscular haemoglobin (MCH)	
	White blood cell (WBC) count with differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
	Haemoglobin	
	Haematocrit	
Clinical Chemistry[a]	Blood urea nitrogen (BUN) Albumin Potassium Creatinine Sodium Calcium Bicarbonate Chloride Glucose (fasting or nonfasting)	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase[b] (ALP) Creatine phosphokinase (CPK) Gamma glutamyl transferase (GGT) Lactate dehydrogenase (LDH) Total and direct bilirubin Total protein
Routine Urinalysis[c]	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)[d] Appearance Colour	
Pregnancy Testing	Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c]	

Urine Drug Screen[c]	Opioids Cocaine Fentanyl[e] Oxycodone Opiates/Morphine Amphetamines Methadone Cannabinoids Barbiturates Benzodiazepines Methamphetamine Phencyclidine
Other Laboratory Tests	Serology (HIV-1 and -2 antibodies, hepatitis B surface antigen [HbsAg], and hepatitis C virus antibody, PTT, and PT with INR)[f]

NOTES:
[a] All events of ALT ≥3× (ULN) and bilirubin ≥2×ULN (>35% direct bilirubin) must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
[b] If alkaline phosphatase is elevated, consider fractionating.
[c] On-site urine testing will be used for this protocol.
[d] 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).
[e] Fentanyl may not show up in all opiate assays and should be assessed separately.
[f] HIV-1/HIV-2, Hepatitis B and Hepatitis C antibody testing to be performed only in the absence of a positive (documented) medical history for these conditions. If there is a positive result for HIV-2/HIV-2 or Hepatitis C, an additional blood draw will be collected at the following site visit for confirmatory testing.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Guidance on Highly Effective Contraception

Not applicable

10.4 Appendix 4: Country-specific Requirements

Not applicable

10.5 Appendix 5: Prohibited Concomitant Therapies

Medications prohibited during the study include, but are not limited to, the following:

Cytochrome P450 3A4 Inhibitors		Cytochrome P450 3A4 Inducers	Cytochrome P450 2C8 Inhibitors	Cytochrome P450 2C8 Inducers
Amiodarone	Ketoconazole	Barbiturates	Gemfibrozil	Rifampicin
Amprenavir	Metronidazole	Carbamazepine	Trimethoprim	
Aprepitant	Mibefradil	Dexamethasone	Glitazones	
Chloramphenicol	Miconazole	Efavirenz	Montelukast	
Cimetidine	Mifepristone	Ethosuximide	Quercetin	
Ciprofloxacin	Nefazodone	Glucocorticoids		
Clarithromycin	Nelfinavir	Glutethimide		
Clotrimazole	Nicardipine	Modafinil		
Cyclosporine	Norfloxacin	Nevirapine		
Delavirdine	Norfluoxetine	Oxcarbazepine		
Diethyl-dithiocarbamate	Propofol	Phenobarbital		
Diltiazem	Quinine	Phenytoin		
Ethinyl estradiol	Ritonavir	Pioglitazone		
Erythromycin	Saquinavir	Primidone		
Fluconazole	Sertraline	Rifabutin		
Fluoxetine	Starfruit	Rifampin		
Fluvoxamine	Telithromycin	Hypericum perforatum		
Gestodene	Troleandomycin	Sulfadimidine		
Grapefruit juice	Verapamil	Sulfinpyrazone		
Imatinib	Voriconazole	Troglitazone		
Indinavir	Zafirlukast	Troleandomycin		
Itraconazole				

Source: http://medicine.iupui.edu/clinpharm/ddis/clinical-table/. Accessed 31 July 2015.

10.6 Appendix 6: Schedule of Assessments – Day -3 to Day 3

Table 11 Schedule of Events – Detailed Inpatient Day -3 to Day 3 With Assessment Windows

Assessment Window	Assessment
Day -3	
Prior to vital signs and clinical laboratory assessments	12-lead ECG
After 12-lead ECG	Vital signs
After 12-lead ECG	Liver function assessment
After 12-lead ECG	Urine pregnancy test
Day -2	
≤15 minutes prior to SUBOXONE dose	PK sample
0 hour	SUBOXONE dose
Day -1	
≤15 minutes prior to SUBOXONE dose	PK sample
0 hour	SUBOXONE dose
+30 minutes *(±5 minutes)*	PK sample
+1 hour *(±5 minutes)*	PK sample
+2 hours *(±5 minutes)*	PK sample
+4 hours *(±5 minutes)*	PK sample
+6 hours *(±15 minutes)*	PK sample
+12 hours *(±15 minutes)*	PK sample
Days 1 to 3	
Pre-Dose SUBLOCADE	
Prior to SUBLOCADE injection	Randomisation criteria reviewed and randomisation
≤60 minutes prior to SUBLOCADE injection	Vital signs
≤30 minutes prior to SUBLOCADE injection	PK sample

Assessment Window	Assessment
0 hour	300 mg SUBLOCADE administration
+1 minute *(±1 minute)*	Injection Site Pain VAS
+5 minutes *(±2 minutes)*	Injection Site Pain VAS
≤10 minutes	Injection site grading
+10 minutes *(±2 minutes)*	Injection Site Pain VAS
+15 minutes *(±2 minutes)*	Injection Site Pain VAS
+30 minutes *(±5 minutes)*	Injection Site Pain VAS
+1-hour Post-Dose SUBLOCADE	
(±5 minutes)	PK sample
(±15 minutes)	Vital signs
(±30 minutes)	Injection site evaluation
+2 hours Post-Dose SUBLOCADE	
(±5 minutes)	PK sample
(±30 minutes)	Injection site evaluation
(±30 minutes)	Injection site grading
+4 hours Post-Dose SUBLOCADE	
(±5 minutes)	PK sample
+6 hours Post-Dose SUBLOCADE	
(±15 minutes)	PK sample
+8 hours Post-Dose SUBLOCADE	
(±15 minutes)	Vital signs
(±15 minutes)	PK sample
+12 hours Post-Dose SUBLOCADE	
(±15 minutes)	PK sample
+16 hours Post-Dose SUBLOCADE	
(±15 minutes)	PK sample
+20 hours Post-Dose SUBLOCADE	
(±15 minutes)	PK sample

Assessment Window	Assessment
+24 hours Post-Dose SUBLOCADE	
(±15 minutes)	PK sample
(±60 minutes)	Vital signs
+28 hours Post-Dose SUBLOCADE	
(±15 minutes)	PK sample
+32 hours Post-Dose SUBLOCADE	
(±15 minutes)	PK sample
+36 hours Post-Dose SUBLOCADE	
(±15 minutes)	PK sample
+40 hours Post-Dose SUBLOCADE	
(±15 minutes)	PK sample
+44 hours Post-Dose SUBLOCADE	
(±15 minutes)	PK sample
+48 hours Post-Dose SUBLOCADE	
(±15 minutes)	PK sample
(±60 minutes)	Vital signs
Anytime during Day 3	Liver function assessment
Discharge from Facility	Following conclusion of all assessments

ECG=electrocardiogram; PK=pharmacokinetic; VAS=visual analogue scale

11 REFERENCES

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th ed. New York: Ardent Media; 2007:24-8.

Ogston-Tuck S. Subcutaneous injection technique: an evidence-based approach. Nursing standard. 2014 Sep 17;29(3).

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.