Study Protocol

NCT03752528

Study Number: INDV-6000-402

Title: Evaluation of Long-term Buprenorphine Plasma Exposure in Subjects Who Received at Least 2 Subcutaneous Injections of Extended-release Buprenorphine (SUBLOCADE™) in Phase III Studies

Protocol Date: 22 April 2019

CLINICAL STUDY PROTOCOL: INDV-6000-402

Protocol Title:	Evaluation of Long-term Buprenorphine Plasma Exposure in Subjects Who Received at Least 2 Subcutaneous Injections of Extended-release Buprenorphine (SUBLOCADE™) in Phase III Studies
Protocol Number:	INDV-6000-402
Product Name:	None
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Original Protocol Date:	Version 3.0 (18 December 2018)
Amendment 1 Date:	Version 4.0 (22 April 2019)

CLINICAL PROTOCOL SIGNATURE PAGE

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Original Protocol Version and Date:	Version 3.0 (18 December 2018)
Amendment 1 Version and Date:	Version 4.0 (22 April 2019)

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

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

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

Signed: [redacted] Date: 22-Apr-2019
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Medical Monitor, Global Medicines Development
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Signed: [redacted] Date: 22-Apr-2019
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INDV-6000-402

Evaluation of Long-term Buprenorphine Plasma Exposure in Subjects Who Received at Least 2 Subcutaneous Injections of Extended-release Buprenorphine (SUBLOCADE™) in Phase III Studies

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol 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 for Harmonisation E6 / Good Clinical Practice (ICH/GCP) guidelines and will make a reasonable effort to complete the study within the time designated.

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

Signed:_____ Date:_____
DD-MMM-YYYY

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

SYNOPSIS

Protocol Title:

Evaluation of Long-term Buprenorphine Plasma Exposure in Subjects Who Received at Least 2 Subcutaneous Injections of Extended-release Buprenorphine (SUBLOCADE™) in Phase III Studies

Protocol Number:

INDV-6000-402

Rationale:

Data indicate that after discontinuing SUBLOCADE™ (extended-release buprenorphine subcutaneous [SC] injection), patients may have detectable concentrations of buprenorphine in plasma and urine for 12 months or longer. The correlation between buprenorphine concentrations in plasma and in urine is currently unknown.

Since previous Phase II/III studies did not evaluate the pharmacokinetics (PK) of buprenorphine beyond 2 months after the last injection of SUBLOCADE, the purpose of the current study is to characterise the long-term plasma exposure to buprenorphine starting at least 12 months after the last injection of SUBLOCADE.

This study will also assess relationships between plasma drug concentrations, free drug concentrations in urine, and urine drug screen (UDS) results for buprenorphine from a diagnostic laboratory. The intent of the study is to provide refined guidance to patients and physicians with respect to long-term exposure to buprenorphine after stopping SUBLOCADE treatment.

Objectives:

The primary objective of this study is to assess long-term plasma exposure to buprenorphine after stopping SUBLOCADE treatment.

Exploratory objectives of this study are the following:

- to refine PK model predictions for long-term plasma exposure to buprenorphine after stopping SUBLOCADE treatment, by developing a more robust population PK model for SUBLOCADE; and
- to assess relationships between drug plasma concentrations, free drug concentrations in urine, and UDS results for buprenorphine from a diagnostic laboratory.

Target Population:

Inclusion Criteria

Each individual must meet all of the following criteria to be enroled in this study:

1. The subject participated in Study RB-US-13-0003 or both Studies RB-US-13-0003 and INDV-6000-301 and received at least 2 SC injections of SUBLOCADE.
2. The subject must be within 12 to 36 months post his or her last SUBLOCADE injection at the time of the Screening visit.

3. Female individuals of childbearing potential (defined as all women who were not surgically sterile or postmenopausal for at least 1 year prior to informed consent) must agree to have a pregnancy test administered prior to enrolment and throughout the study. Pregnancy will not prohibit them from participation in the study.
4. The subject must be willing to adhere to study procedures and provide written informed consent prior to the start of any study procedures.

Exclusion Criteria

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

1. The subject received SUBLOCADE or any other long-acting buprenorphine product at any time after ending their participation in Study RB-US-13-0003 or Study INDV-6000-301.
2. The subject has taken any buprenorphine (prescribed or illicit) within 3 weeks prior to the Screening visit.

This study is divided into 2 parts, Part A and Part B. Subjects who meet all inclusion criteria and meet none of the exclusion criteria will be considered eligible to enrol in Part A. See Study Design section below for criteria for continuation into Part B.

Number of Subjects:

Approximately 60 male or female subjects shall be enroled in Part A.

A maximum of 30 Part A subjects will proceed into Part B (continuation part of the study).

Study Design:

This multicentre investigation will enrol subjects who participated in Study RB-US-13-0003 or both Studies RB-US-13-0003 and INDV-6000-301 and who received at least 2 SC injections of SUBLOCADE.

Part A will include all subjects who meet inclusion criteria and do not meet exclusion criteria. Data from subjects in Part A will be used to ensure a fully representative dataset for the distribution of plasma and urine data in the overall population within the time frame investigated (i.e., 12 to 36 months post the last SUBLOCADE injection). Buprenorphine plasma concentration data will be used to refine the existing population PK model for SUBLOCADE developed from Phase II/III study data, to provide accurate predictions for long-term plasma exposure to buprenorphine after discontinuation of SUBLOCADE treatment.

Part B will include subjects from Part A who meet continuation criteria as detailed below until a maximum of 30 subjects are enroled. Data from subjects in Part B will inform the consistency of the PK profiles over time, the stability of urine-to-plasma ratios and norbuprenorphine-to-buprenorphine ratios in urine.

Part A

Following Screening, eligible subjects who meet inclusion criteria and do not meet exclusion criteria will undergo Visit 1 assessments (same day as Screening) as follows:

- Collection of a urine sample for determination of free buprenorphine and free norbuprenorphine concentrations; qualitative UDS for opioids, including

buprenorphine; quantitative UDS for buprenorphine, norbuprenorphine and naloxone; and determination of creatinine concentration.

- Collection of a blood sample for the determination of buprenorphine and norbuprenorphine plasma concentrations.

Part B

Results on the quantitative UDS performed at Visit 1 will determine enrolment in Part B: subjects who provide a quantifiable (i.e., positive) result for buprenorphine and/or norbuprenorphine and a non-quantifiable (i.e., negative) result for naloxone will meet continuation criteria to move on to Part B if Part B is still open to enrolment. Part B will consist of 2 visits with 30 days (±7 days) between the visits.

At each visit, the same assessments as in Part A will be performed. In addition, the subject will answer a question regarding his or her illicit use of buprenorphine within the last 14 days.

The subject will continue the study until he or she meets one of the following criteria:

- the subject completes both visits in Part B;
- the subject discontinues study participation for any reason or misses the 2 visits, or the Sponsor decides to terminate the subject's participation or modifies the duration of the study.

If subjects initiate treatment with SUBLOCADE or any other long-acting buprenorphine product during the study, they will be discontinued from the study and no further samples will be collected. Subjects who start any non-buprenorphine medication-assisted treatment or trans-mucosal buprenorphine treatment will not be discontinued from the study.

Part B may meet enrolment and be considered closed to new subjects while Part A is still open to enrolment.

Duration of Treatment:
This is an observational study with no drug intervention.

Primary Endpoint:

The primary endpoint will consist of a plot representing individual plasma concentrations of buprenorphine and norbuprenorphine over time using the time elapsed from the last SUBLOCADE dose.

Exploratory Endpoints:

Exploratory endpoints will include the following:

- the parameter estimates of the refined population PK model for buprenorphine;
- a plot representing individual urine concentrations of buprenorphine and norbuprenorphine over time using the time elapsed from the last SUBLOCADE dose;
- norbuprenorphine-to-buprenorphine concentration ratios in plasma and urine over time;
- plasma-to-urine concentration ratios for buprenorphine and norbuprenorphine over time.

Other exploratory endpoints will be derived from the PK model; for example, the distribution of times for which buprenorphine plasma concentration are above the lower limit of quantification for the 2 dosing regimens of SUBLOCADE.

Measures of Interest:

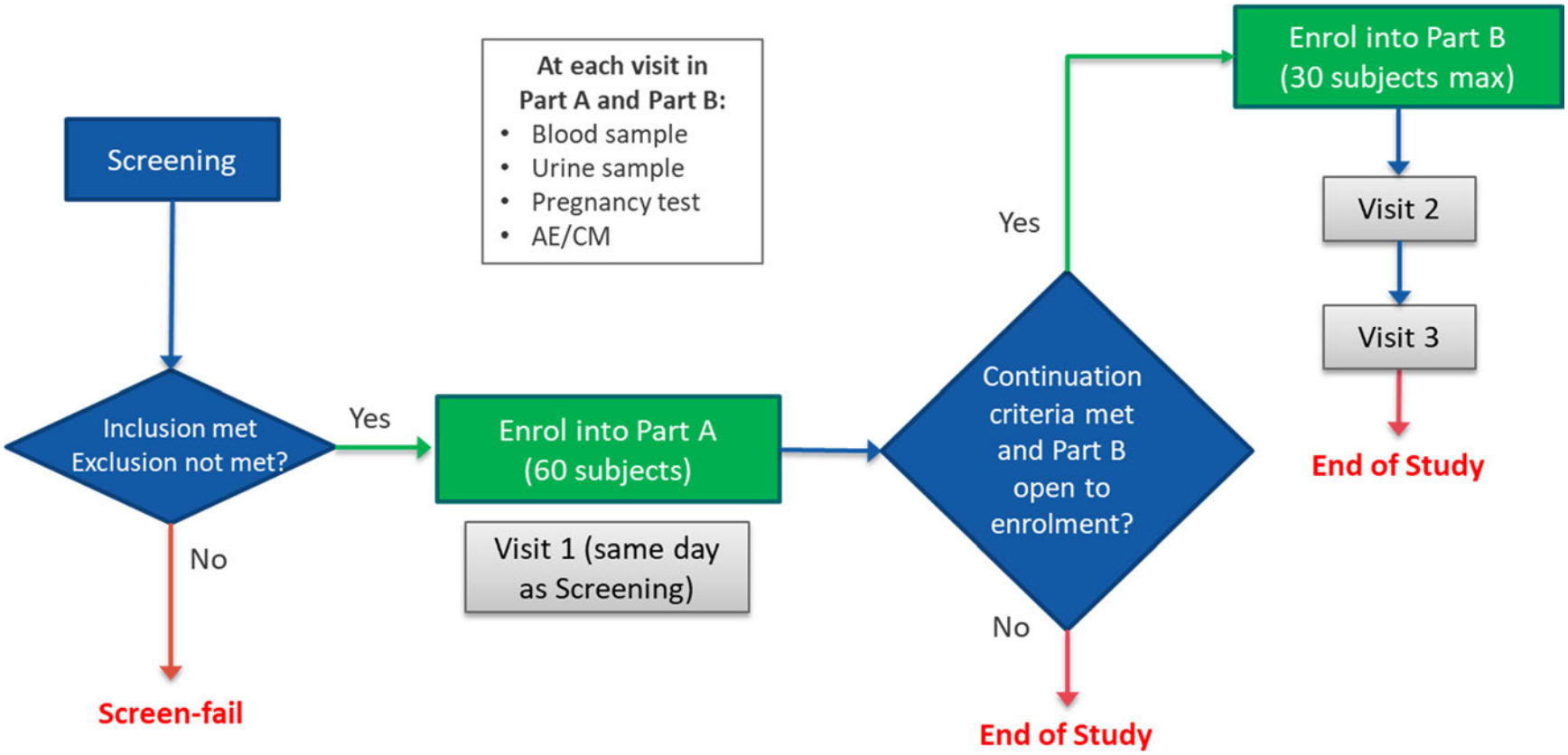
The following PK assessments will be performed at each visit of Part A or Part B:

- Collection of a blood sample for the determination of buprenorphine and norbuprenorphine concentrations in plasma;
- Collection of a urine sample:
  - Aliquots (primary and back-up) will be sent to the bioanalytical laboratory for the determination of free buprenorphine and free norbuprenorphine concentrations in urine.
  - Additional aliquots will be prepared and sent to the diagnostic laboratory who will perform 3 analyses: 1) qualitative UDS for buprenorphine; 2) quantitative UDS for buprenorphine, norbuprenorphine and naloxone (quantifiable concentrations of buprenorphine and/or norbuprenorphine on this assessment will indicate a positive result); and 3) determination of creatinine concentration in urine.

Clinical assessments will include a qualitative UDS for opioids plus self-reported use of illicit buprenorphine.

Safety will be assessed based on adverse events (including serious adverse events) associated with study assessments and/or study conduct. Concomitant medications will also be collected.

STUDY SCHEMATIC



AE/CM=adverse events and concomitant medications; max=maximum

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LIST OF ABBREVIATIONS

AE	adverse event
CRF/eCRF	case report form/electronic case report form
CSR	clinical study report
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
MAT	medication-assisted treatment
MedDRA	Medical Dictionary For Regulatory Activities
OUD	opioid use disorder
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOP	standard operating procedure
UDS	urine drug screen
WHO	World Health Organization

1 INTRODUCTION AND RATIONALE

1.1 Background

Opioid use disorder (OUD) is a chronic, relapsing, neurobehavioral syndrome characterised by repeated, compulsive seeking or use of an opioid despite adverse social psychological and physical consequences (Substance Abuse and Mental Health Services Administration 2004). Medication-assisted treatment (MAT), which combines counselling/behavioural therapy with medications to provide a whole-patient approach, is recommended by treatment guidelines as the current standard of care for OUD (Kampman 2015).

SUBLOCADE™ (extended-release buprenorphine subcutaneous [SC] injection) is an extended-release formulation of buprenorphine, a mu-opioid receptor partial agonist. SUBLOCADE is currently indicated for the treatment of moderate to severe OUD in patients who have initiated treatment with a transmucosal buprenorphine-containing product to suppress opioid withdrawal signs and symptoms. SUBLOCADE should be used as a part of a complete treatment program that includes counselling and psychosocial support.

SUBLOCADE is administered once monthly and provides sustained plasma concentrations of buprenorphine over the dosing interval. SUBLOCADE uses buprenorphine and the ATRIGEL® Delivery System, which consists of a biodegradable polymer poly(DL-lactide-co-glycolide) with a carboxylic acid end group, dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone. SUBLOCADE is injected as a solution, and subsequent precipitation of the polymer creates a solid depot containing the buprenorphine. After initial formation of the depot, buprenorphine is slowly released via diffusion from, and the biodegradation of, the depot.

1.2 Clinical Pharmacology Information

After SUBLOCADE injection in clinical studies, an initial buprenorphine peak was observed at approximately 24 hours post-dose. The initial peak was followed by a decline in plasma concentrations to a plateau throughout the monthly dosing interval, consistent with the slow release of buprenorphine from the SC depot. The apparent terminal plasma half-life of buprenorphine following SC injection of SUBLOCADE ranged between 43 to 60 days. Steady-state was achieved at 4 to 6 months following repeated monthly SC injections.

Buprenorphine is metabolized to its major metabolite, norbuprenorphine, primarily by cytochrome P450 3A4 and, to a lesser extent, by cytochrome P450 2C8. Norbuprenorphine can further undergo glucuronidation. Norbuprenorphine has been found to bind to mu-opioid receptors in vitro; however, norbuprenorphine is expected to have negligible contribution to brain mu-opioid receptor occupancy given its limited ability to cross the blood-brain barrier (Ohtani 2007) and has not been studied clinically for opioid-like activity. Norbuprenorphine steady-state plasma concentrations in humans after SC injection of SUBLOCADE were low compared with buprenorphine. The ratio of norbuprenorphine/buprenorphine areas under the plasma concentration-time curve (AUC) in a repeat-dose study (RB-US-12-0005) was 0.2 to 0.4, i.e., much lower than for transmucosal buprenorphine (ratio of 1.3-3.2 in the same study) due to the lack of first-pass effect.

1.3 Study Rationale

Data from population pharmacokinetic (PK) modelling and individual case studies indicate that patients may have detectable concentrations of buprenorphine in plasma and urine for 12 months or longer after discontinuation of SUBLOCADE treatment. The correlation between plasma concentrations of buprenorphine and those detectable in urine is currently unknown.

Since previous Phase II/III studies did not evaluate the PK of buprenorphine beyond 2 months after the last dose of SUBLOCADE, the purpose of the current study is to characterise the long-term plasma exposure to buprenorphine starting at least 12 months after the last SUBLOCADE injection.

The study will be organised into 2 parts: Part A and Part B.

- Part A (See Section 4.1): Collect single plasma and urine samples in 60 subjects who received at least 2 SUBLOCADE injections in the Phase III studies. This number of subjects is expected to provide a reasonable description of the distribution of plasma and urine concentration data in the overall population over the timeframe investigated (i.e., 12 to 36 months post the last SUBLOCADE injection), given the low-moderate interindividual variability (~30%) observed for SUBLOCADE PK in previous studies. The number of subjects to be enroled in Part A is limited by the availability of patients who received at least 2 SC injections of SUBLOCADE in Phase III studies and who remain in the time window targeted for enrolment in the current study. The data collected in Part A will inform the long-term plasma exposure of buprenorphine after the last SUBLOCADE injection as well as the percentage of urine samples negative and positive for buprenorphine over that time period.

- Part B: Collect additional plasma and urine samples from 30 subjects who participated in Part A and who provided positive results for buprenorphine and/or norbuprenorphine on the quantitative urine drug screen (UDS) performed at Visit 1. These data will inform the consistency of the plasma and urine PK data over time. It is anticipated that approximately 30 subjects will be sufficient for this purpose. The final number of subjects will depend on results from quantitative buprenorphine UDS in Part A.

The totality of the data collected in Parts A and B will be used to refine the existing population PK model developed from Phase II/III study data, and to provide accurate model predictions for long-term plasma exposure to buprenorphine after discontinuation of SUBLOCADE treatment. Additionally, data will be used to explore the relationships between plasma drug concentrations, free drug concentrations in urine, and UDS results for buprenorphine from a diagnostic laboratory. Norbuprenorphine-to-buprenorphine ratios will be assessed both in plasma and urine, as well as plasma-to-urine ratios for both analytes.

The intent of the study is to provide refined guidance to patients and physicians with respect to long-term exposure to buprenorphine after stopping SUBLOCADE treatment.

1.4 Risk-Benefit Assessment

This is an observational study with no drug intervention. The risks in this study are minimal, given that assessments are based on a single blood sample and a single urine sample for subjects in Part A. Subjects progressing to Part B will provide a maximum of 2 additional blood samples and 2 additional urine samples taken at 2 subsequent monthly visits. The risks involved in collecting venous blood samples may include possible bruising, redness and swelling around the site of blood withdraw; bleeding at the site; feeling of light-headedness when the blood is drawn; and rarely, an infection at the site. Results of urine assessments relative to buprenorphine and other opioids will remain confidential.

The study does not provide direct benefit to the study subjects; however the results of the study will inform patients and physicians on how long buprenorphine remains at quantifiable concentrations in plasma after the last dose of SUBLOCADE, as well as clarifying the relationship with positive UDS for buprenorphine.

Based on ongoing review of the data, the Sponsor reserves the right to modify the duration of the study at any time.

The study will be carried out in accordance to the protocol and with local legal and regulatory requirements, International Council for Harmonisation E6 / Good Clinical Practice (ICH/GCP) guidelines and all applicable subject privacy requirements.

2 STUDY OBJECTIVES

2.1 Primary

The primary objective of this study is to assess long-term plasma exposure to buprenorphine after stopping SUBLOCADE treatment.

2.2 Exploratory

The exploratory objectives of this study are the following:

- to refine PK model predictions for long-term plasma exposure to buprenorphine after stopping SUBLOCADE treatment, by developing a more robust population PK model for SUBLOCADE; and
- to assess relationships between drug plasma concentrations, free drug concentrations in urine, and UDS results for buprenorphine from a diagnostic laboratory.

3 STUDY ENDPOINTS

The primary endpoint will consist of a plot representing individual plasma concentrations of buprenorphine and norbuprenorphine over time using the time elapsed from the last SUBLOCADE dose.

Exploratory endpoints will include the following:

- the parameter estimates of the refined population PK model for buprenorphine;
- a plot representing individual urine concentrations of buprenorphine and norbuprenorphine over time using the time elapsed from the last SUBLOCADE dose;
- norbuprenorphine-to-buprenorphine concentration ratios in plasma and urine over time;
- plasma-to-urine concentration ratios for buprenorphine and norbuprenorphine over time.

Other exploratory endpoints will be derived from the PK model, for example, the distribution of times for which buprenorphine plasma concentrations are above the lower limit of quantification for the 2 dosing regimens of SUBLOCADE.

4 STUDY PLAN

4.1 Study Design

This multicentre investigation will enrol subjects who participated in Study RB-US-13-0003 or both Studies RB-US-13-0003 and INDV-6000-301 and who received at least 2 SC injections of SUBLOCADE. This study is divided into 2 parts, Part A and Part B.

Part A

Following Screening, eligible subjects who meet inclusion criteria and do not meet exclusion criteria will undergo Visit 1 assessments (same day as Screening) including the following:

- collection of a urine sample for determination of free buprenorphine and free norbuprenorphine concentrations; qualitative UDS for opioids, including buprenorphine; quantitative UDS for buprenorphine, norbuprenorphine and naloxone; and determination of creatinine concentration.

- collection of a blood sample for the determination of buprenorphine and norbuprenorphine plasma concentrations.

Part B

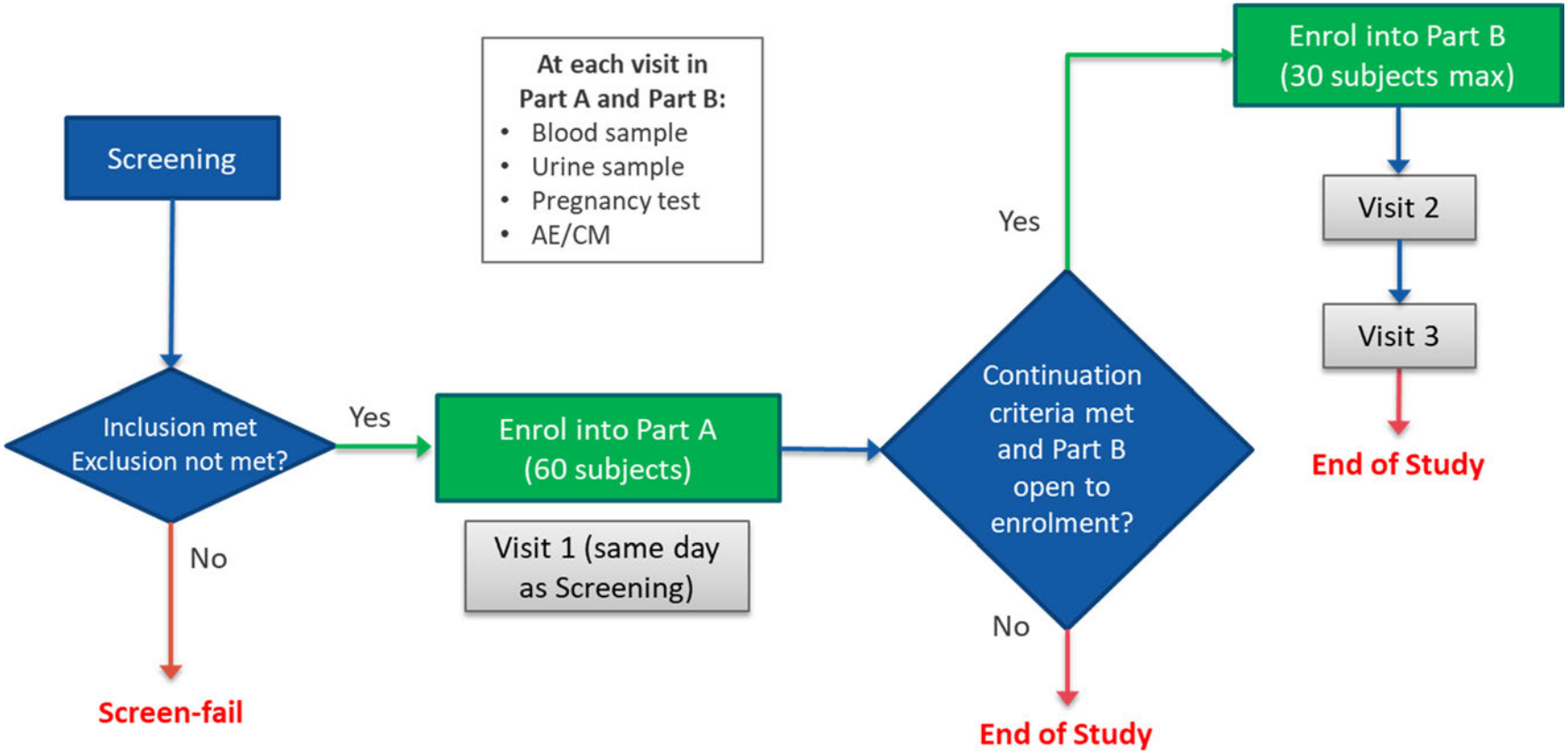
Results on the quantitative UDS performed at Visit 1 will determine enrolment in Part B: subjects who provide a quantifiable (i.e., positive) result for buprenorphine and/or norbuprenorphine and a non-quantifiable (i.e., negative) result for naloxone will meet continuation criteria to move on to Part B if Part B is still open to enrolment. Part B will consist of 2 visits, with 30 days (±7 days) between the visits.

At each visit, the same assessments as in Part A will be performed. In addition, the subject will answer a question regarding his or her illicit use of buprenorphine within the last 14 days.

Part B may meet enrolment and be considered closed to new subjects while Part A is still open to enrolment.

A schematic depicting the study design is in Figure 1.

Figure 1 Study Schematic



AE/CM=adverse events and concomitant medications; max=maximum

4.2 Schedule of Events

A complete list of procedures and assessments is included in Appendix 1 – Schedule of Events.

4.3 Duration of Treatment

This is an observational study with no drug intervention.

Subjects will participate in the study for a maximum study duration of 2 months (+2 weeks).

The total duration of the study for each subject will be as follows:

- If, at Visit 1 (Part A), the subject achieves a negative result for both buprenorphine and norbuprenorphine quantitative UDS, regardless of naloxone result, the duration of his or her participation will be 1 day.

- For subjects who participate in Part B, if the subject completes both visits in Part B, the maximum duration of his or her study participation would be 2 months (+2 weeks).

Based on ongoing review of the data, the Sponsor reserves the right to modify the duration of the study at any time.

5 STUDY POPULATION SELECTION

5.1 Number of Subjects

Approximately 60 male or female subjects shall be enroled in Part A.

A maximum of 30 Part A subjects will proceed into Part B (continuation part of the study).

Subjects who withdraw or are discontinued from the study will not be replaced.

5.2 Inclusion Criteria

Part A

Each individual must meet the following criteria to be enroled in Part A of this study:

1. The subject participated in Study RB-US-13-0003 or both Studies RB-US-13-0003 and INDV-6000-301 and received at least 2 SC injections of SUBLOCADE.

2. The subject must be within 12 to 36 months post his or her last SUBLOCADE injection at the time of the Screening visit.

3. Female individuals of childbearing potential (defined as all women who were not surgically sterile or postmenopausal for at least 1 year prior to informed consent) must agree to have a pregnancy test administered prior to enrolment and throughout the study. Pregnancy will not prohibit them from participation in the study.

4. The subject must be willing to adhere to study procedures and provide written informed consent prior to the start of any study procedures.

5.3 Exclusion Criteria

Part A

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

1. The subject received SUBLOCADE or any other long-acting buprenorphine product at any time after ending their participation in Study RB-US-13-0003 or Study INDV-6000-301.

2. The subject has taken any buprenorphine (prescribed or illicit) within 3 weeks prior to the Screening visit.

5.4 Part B Continuation Criterion

Results on the quantitative UDS performed at Visit 1 will determine enrolment in Part B:

- Subjects who provide a quantifiable (i.e., positive) result for buprenorphine and/or norbuprenorphine and a non-quantifiable (i.e., negative) result for naloxone will continue into Part B of the study if Part B is still open to enrolment.

- Subjects who achieve negative results for both buprenorphine and norbuprenorphine quantitative UDS (irrespective of naloxone result) at Visit 1 will conclude their study participation, as will subjects who achieve a positive result for buprenorphine and/or norbuprenorphine and a positive result for naloxone on the quantitative UDS performed at Visit 1.

5.5 Prohibited Concomitant Therapies

Concomitant medications will be collected from Visit 1 until the last visit at the time points listed in Appendix 1 – Schedule of Events. Any concomitant medications (including herbal preparations) taken during the study will be recorded in the source documents and in the electronic case report form (eCRF). Any changes in concomitant therapy during the study will be documented, including cessation of therapy, initiation of therapy and dose changes.

5.5.1 Permitted Concomitant Therapies

The Investigator may prescribe concomitant medications or treatments deemed necessary to the subject without any impact on study participation, with the exception of those medications defined in Section 5.5.2 of this protocol.

Subjects who start any non-buprenorphine MAT or transmucosal buprenorphine treatment will not be discontinued from the study. Information on MAT initiation, dosing regimen, potential changes in dose and cessation of therapy must be documented.

5.5.2 Prohibited Concomitant Therapies

If subjects initiate treatment with SUBLOCADE or any other long-acting buprenorphine product during the study, they will be discontinued from the study and no further samples will be collected.

6 STUDY CONDUCT

Study assessments and procedures, including the timing of assessments, are summarised in Appendix 1 – Schedule of Events.

6.1 Subject Enrolment

Study participation begins once written informed consent is obtained. Subject identification numbers will be carried over from the previous Phase III SUBLOCADE study in which the subject participated. The subject identification numbers will be used to identify the subject during the screening process and throughout study participation.

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

6.2 Screen Failure

A subject will be considered a screen failure if written informed consent is obtained but the subject does not meet eligibility criteria for Part A.

6.3 Subject Completion

A completed subject for Part A is one who has completed all of the plasma and urine assessments for Part A (i.e., Visit 1).

A completed subject for Part B is one who has completed all of the plasma and urine assessments at both visits for Part B.

6.4 Withdrawal and Stopping Criteria

Part A consists of a single visit (Visit 1) so there are no withdrawal or stopping criteria except subject withdrawal of consent (see Section 6.4.2).

6.4.1 Subject Withdrawal from the Study

For subjects who participate in Part B, the subject will continue the study until he or she meets one of the following criteria:

- The subject completes both visits in Part B.
- The subject discontinues study participation for any reason or misses the 2 visits, or the Sponsor decides to terminate the subject's participation or modifies the duration of the study.

Part B may meet enrolment and be considered closed to new subjects while Part A is still open to enrolment.

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

6.4.2 Subject Withdrawal of Consent

If a subject withdraws consent, he or she will no longer be followed for study assessments and will be considered withdrawn from the study. The primary reason for withdrawing from the study must be entered in the eCRF.

6.4.3 Subjects Lost to Follow-up

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

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

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

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

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

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

7 STUDY SUSPENSION OR TERMINATION

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

If required by applicable regulations, the Investigator must inform the Institutional Review Board (IRB) promptly and provide the reason(s) for the suspension or termination.

8 DESCRIPTION OF STUDY PROCEDURES

Study assessments and procedures, including the timing of assessments, are summarised in Appendix 1 – Schedule of Events. Further details on PK, clinical and safety assessments are provided in Sections 8.2, 8.3 and 8.4, respectively.

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

8.1 Demographics and Medical History

A detailed medical and psychiatric history since the end of the previous participation in Phase III SUBLOCADE study will be obtained during the Screening period. This will include information regarding the subject's history of relevant medical conditions, diagnoses, procedures, treatments and any other noteworthy medical information. Height and body weight will also be collected, and body mass index will be calculated in the eCRF. Any updates to medical history information made available during the course of the study will be captured. Demographics, medical and psychiatric history will be recorded in the source documents and the eCRF per Appendix 1 – Schedule of Events.

8.2 Pharmacokinetic and Clinical Assessments

Part A

Visit 1 (same day as Screening) PK and clinical assessments will be as follows:

- collection of a blood sample for the determination of buprenorphine and norbuprenorphine plasma concentrations.
- collection of a urine sample for determination of free buprenorphine and free norbuprenorphine concentrations; qualitative UDS for opioids, including buprenorphine; quantitative UDS for buprenorphine, norbuprenorphine and naloxone; and determination of creatinine concentration.

Part B

At each visit, the same assessments as in Part A will be performed:

- collection of a blood sample for the determination of buprenorphine and norbuprenorphine plasma concentrations.

- collection of a urine sample for determination of free buprenorphine and free norbuprenorphine concentrations; qualitative UDS for opioids, including buprenorphine; quantitative UDS for buprenorphine, norbuprenorphine and naloxone; and determination of creatinine concentration.

In addition, the subject will answer a question regarding his or her illicit use of buprenorphine within the last 14 days.

8.2.1 Sample Collection, Storage, and Shipping

Details for the collection, preparation, storage and shipment of laboratory specimens will be outlined in the laboratory manual.

8.2.2 Plasma Samples for Pharmacokinetic Analysis

Blood samples for PK analysis of buprenorphine and norbuprenorphine will be collected at the time points listed in Appendix 1 – Schedule of Events. The actual date and time of each sample collection will be documented. For each PK sample, 6 mL of blood will be collected into K_2-EDTA tubes. After centrifugation of the tubes, the resulting plasma will be separated into aliquots (primary and back-up). The primary aliquot will be sent to the bioanalytical laboratory for the determination of buprenorphine and norbuprenorphine plasma concentrations. Details about sample processing, storage and shipping procedures are provided in the laboratory manual.

8.2.3 Urine Samples for Pharmacokinetic Analysis and Qualitative UDS

Urine samples will be collected at the time points listed in Appendix 1 – Schedule of Events. Efforts will be made to collect urine samples under similar conditions across visits.

The following aliquots will be prepared from each urine sample:

- Aliquots (primary and back-up) will be sent to the bioanalytical laboratory for the determination of free buprenorphine and free norbuprenorphine concentrations in urine.

- Additional aliquots will be prepared and sent to the diagnostic laboratory who will perform 3 analyses: 1) qualitative UDS for opioids, including buprenorphine; 2) quantitative UDS for buprenorphine, norbuprenorphine and naloxone; and 3) determination of creatinine concentration in urine.

All details related to urine collection (including volume of urine collected), sample processing (preparation of aliquots), storage and shipping procedures are provided in the laboratory manual.

8.2.4 Sample Analysis

The analysis of plasma samples will be performed by a bioanalytical laboratory using a validated liquid chromatography with tandem mass spectrometry method for the determination of buprenorphine and norbuprenorphine concentrations in plasma.

The analysis of urine samples will be conducted by 2 laboratories:

- a bioanalytical laboratory for the determination of free buprenorphine and free norbuprenorphine concentrations in urine, using a validated liquid chromatography with tandem mass spectrometry method;

- a diagnostic laboratory for 1) qualitative UDS for opioids, including buprenorphine; 2) quantitative UDS for buprenorphine, norbuprenorphine and naloxone; and 3) determination of creatinine concentration in urine.

Raw data generated by the bioanalytical laboratory will be archived at the bioanalytical site. The results of analyses performed by the diagnostic laboratory will be archived as described in the laboratory manual. Additional methodologies will be summarised in the clinical study report (CSR).

8.3 Clinical Assessments

Clinical assessments will include UDS for opioids (described in Section 8.2) and self-reported use of illicit buprenorphine within the last 14 days.

8.4 Safety Assessments

All adverse events (AE) associated with study assessments and/or study conduct will be collected using the Adverse Event eCRF. All serious AEs (SAEs) associated with the study assessments and/or study conduct will be collected using the Safety Information Collection Form.

Concomitant medications will be collected, including any prescribed MAT (inclusive of any MATs that lead to study discontinuation, such as long-acting buprenorphine treatment).

Illicit use of buprenorphine will be captured separately outside of the Concomitant Medication eCRF.

See Section 12 for details of pregnancy assessments.

8.5 Appropriateness of Measurements

All of the safety assessments in this protocol are standard. The PK assessments have been used for quantification of buprenorphine and norbuprenorphine concentrations in plasma in previous registration studies for SUBLOCADE. The PK assessments are being used to assess the long-term plasma exposure to buprenorphine after stopping SUBLOCADE treatment and to refine the existing population PK model of SUBLOCADE. Some of the UDS assessments were also used in these prior registration studies. Together with plasma concentration data, urine results will be used to evaluate the relationships between drug plasma concentrations, free drug concentrations in urine, and UDS results for buprenorphine from a diagnostic laboratory.

8.6 Protocol Deviations

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

9 STUDY DRUG MANAGEMENT

This is an observational study with no drug intervention.

10 ADVERSE EVENTS

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

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In addition, any AE or SAE of which the Investigator becomes aware that pertains to SUBLOCADE or SUBOXONE use, or related to participation in a previous SUBLOCADE clinical study, will be reported via completion of the Safety Information Collection Form and that form will be sent to the following email address: PatientSafetyNA@indivior.com.

Events meeting the definition of an AE associated with study assessments and/or study conduct include the following:

- new condition detected after study assessment and/or associated with study conduct even though the AE may have been present prior to the study assessment or study participation;
- exacerbation of a pre-existing condition (including intensification of a condition and/or an increase in frequency) resulting from a study assessment and/or study conduct;
- any safety assessments resulting from a study assessment and/or study conduct felt to be clinically significant in the opinion of the Investigator (including those that worsen from baseline);
- symptoms and/or clinical sequelae resulting from a study assessment and/or study conduct that resulted in intervention.

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

- the disease/disorder being studied, or expected progression, signs, or symptoms of the disease being studied, unless more severe than expected for the subject's condition;
- medical or surgical procedures; the condition that leads to the procedure is an AE;
- situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, hospitalization for elective surgery, hospitalization for observation in the absence of an AE);
- anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.1 Assessment of Adverse Events

The Investigator is ultimately responsible for assessing and reporting all AEs as outlined in the protocol. The assessment and reporting of AEs may be delegated to a medically qualified sub-Investigator, trained on this study protocol, who is listed on the delegation of authority log.

Adverse events should be volunteered by the subject or obtained from observation of the subject at a site visit. If an event requires intervention, or if in the opinion of the Investigator it is clinically significant, then it will be reported as an AE (using the Adverse Event eCRF).

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

10.1.1 Time Period for Collecting Adverse Events

Adverse events will be collected from the time of signed informed consent until completion of the subject's last visit.

Subjects with SAEs related to study procedures ongoing at the end of the study or after early termination will be followed by the Investigator until stabilization or resolution. If a subject experiences the onset of an SAE assessed by the Investigator as related to study procedures within a period of 30 days following study completion or withdrawal, the Investigator will follow the procedures defined in Section 10 and Section 11 for assessing, documenting, and reporting these events.

10.1.2 Assessment of Intensity

The term "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

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

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

10.1.3 Assessment of Causality

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

The following categories will be used to define the relationship of an AE to study assessments/conduct:

Not Related:	Data are available to identify a clear alternative cause for the AE other than assessments/conduct.
Related:	The cause of the AE is related to assessments/conduct, and cannot be reasonably explained by other factors (e.g., the subject's clinical state, concomitant therapy, and/or other interventions).

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

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

11 SERIOUS ADVERSE EVENTS

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

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

- death;
- life-threatening;
- inpatient hospitalization or prolongation of existing hospitalization;
- persistent or significant disability/incapacity;
- congenital anomaly/birth defect in the offspring of a subject who underwent study procedures in the current study;
- other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
    - intensive treatment in an emergency room or at home for allergic bronchospasm
    - blood dyscrasias or convulsions that do not result in inpatient hospitalization

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

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

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

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

11.1 Documenting Serious Adverse Events

All SAEs should be submitted within 24 hours of the Investigator becoming aware of the event.

Only SAEs associated with study assessments and/or study conduct will be collected using the Safety Information Collection Form..

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

The Investigator should not send photocopies of the subject's medical records to Indivior in lieu of completion of the Safety Information Collection Form. However, there may be cases where copies of medical records are requested by Indivior or designated representative. In this instance, all subject identifiers, with the exception of subject number, will be redacted on the copies of the medical records prior to submission to Indivior.

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

11.2 Reporting Serious Adverse Events

11.2.1 Investigator Reporting of Serious Adverse Events

Once the Investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to Indivior (or designated representative) by the Investigator (or designee) within 24 hours from first being aware of the event by completing the appropriate portion of the eCRF(s) and the Safety Information Collection Form. Any follow-up information on a previously reported SAE will also be reported to Indivior within 24 hours by updating the appropriate eCRF(s) or Safety Information Collection Form.

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

The Safety Information Collection Form should be completed and submitted to Indivior Pharmacovigilance via email or fax:

Email: PatientSafetyNA@indivior.com
Fax: (804) 423-8951
Indivior
10710 Midlothian Turnpike, Suite 430

North Chesterfield, VA 23235

11.2.2 Regulatory Reporting Requirements for Serious Adverse Events

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

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

11.2.3 Overdose

This is an observational study with no drug intervention.

12 PREGNANCY

Women of childbearing potential will undergo urine pregnancy tests at each visit. Pregnancy prior to or during the study will not lead to discontinuation. At the time of informed consent, women who are or could become pregnant will also be asked to allow the Sponsor to follow their pregnancy for up to 2 years post-partum. If subjects do not consent to allow their pregnancy to be followed, they can still participate in the study.

If a subject is pregnant and tests negative for buprenorphine and/or norbuprenorphine on quantitative UDS at Visit 1, no further follow-up will be required from the Sponsor on their pregnancy.

In the case of pregnancy, the Investigator or designee will notify Indivior Pharmacovigilance by completing the Safety Information Collection Form within 1 business day. Follow-up information will also be reported via the Safety Information Collection Form.

The Safety Information Collection Form should be completed and submitted to Indivior Pharmacovigilance via email or fax:

Email: PatientSafetyNA@indivior.com
Fax: (804) 423-8951
Indivior
10710 Midlothian Turnpike, Suite 430
North Chesterfield, VA 23235

13 DATA MANAGEMENT

13.1 Data Collection and Management

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

13.1.1 Database Quality Assurance

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

13.1.2 Source Documents

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

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

14 STATISTICS

14.1 General Procedures

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

Summary statistics on continuous and categorical variables will be calculated when applicable. Continuous variables will be summarised using descriptive statistics such as mean, standard deviation, median, minimum, and maximum. Categorical variables will be reported as frequency counts (including number missing) and the percentage of subjects in corresponding categories. Individual subject data will be presented by subject in data listings. Data listings will include all data collected from the initial Screening visit to the end of the study for all subjects enroled. A Statistical Analysis Plan (SAP) will be prepared after the protocol is approved and before database lock occurs. The SAP will provide further details regarding analysis. Additional unplanned analyses may be required after all planned analyses have been completed. Any deviations from the analyses described below will be outlined in the SAP. Any unplanned analyses will be clearly identified in the CSR.

No formal statistical testing (p-values, confidence intervals) will be computed due to small sample size.

Part A

Data listings for individual plasma and urine results will be provided once all subjects have completed Part A. Individual plasma/urine concentration data will be plotted over time using time elapsed from the last SUBLOCADE dose.

Part B

As for Part A, individual data listings for plasma and urine results and graphical representation of the data will be provided.

14.2 Sample Size

The sample size is based on practical considerations and no statistical power is calculated. Approximately 60 subjects will be enroled in Part A. This number of subjects is expected to provide a reasonable description of the distribution of plasma and urine concentration data in the overall population over the timeframe investigated (i.e., 12 to 36 months post the last SUBLOCADE injection), given the low-moderate interindividual variability (~30%) observed for SUBLOCADE PK in previous studies. The number of subjects to be enroled in Part A is also limited by the availability of patients who received at least 2 SC injections of SUBLOCADE in Phase III studies and who remain in the time window targeted for enrolment in the current study. A maximum of 30 Part A subjects will proceed to Part B; it is anticipated that approximately 30 subjects will be sufficient to address the objectives for Part B. The final number of subjects will depend on results from quantitative buprenorphine UDS in Part A. Data will be reviewed on an ongoing basis.

14.3 Analysis Populations

All subjects enroled in Part A will be included in the Full Analysis Set – Part A and all subjects enroled in Part B will be included in the Full Analysis Set – Part B. The Full Analysis Set consists of all subjects who received at least 2 SC doses of SUBLOCADE in Study RB-US-13-0003 or both Studies RB-US-13-0003 and INDV-6000-301 and was enroled in the current study. This will be the analysis population for all analyses.

14.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics, (e.g., sex, race, age, weight and height) will be summarised by treatment group using descriptive statistics. Qualitative variables, (e.g., sex and race) will be summarised using frequencies; quantitative variables, (e.g., age, weight and height) will be summarised using descriptive statistics.

14.5 Analysis of Pharmacokinetic Data

A descriptive representation of PK data (plasma, urine) over time will be provided. Individual plasma/ urine concentration data will be plotted over time using the time elapsed from the last SUBLOCADE dose. Concentrations of buprenorphine and norbuprenorphine in urine (from quantitative UDS or free drug concentration assessments) will be presented with and without correction by creatinine concentration in urine. The purpose of the correction by creatinine urine concentration is to correct for urinary dilution.

Norbuprenorphine-to-buprenorphine ratios will be calculated from plasma drug concentrations, free drug concentrations in urine, and quantitative UDS results from the diagnostic laboratory. Relationships between plasma and urine drug concentrations will also be explored. Plots will be constructed to assess the consistency of those ratios over time.

Furthermore, the sparse plasma samples collected during Parts A and B will be used to refine the existing population PK model for SUBLOCADE developed from the combined analysis of the multiple-ascending-dose study (RB-US-12-0005) and the 2 Phase III studies (RB-US-13-0001 and RB-US-13-0003) (modelling report, IND-6000-M05). The purpose is to characterise the long-term decrease in buprenorphine plasma concentration following discontinuation of SUBLOCADE treatment. Buprenorphine plasma concentrations below the lower limit of quantification will be handled using appropriate likelihood-based methodology. The final model will be used to derive population predictions for the 2 dosing regimens of SUBLOCADE and derive endpoints such as the distribution of times for which buprenorphine plasma concentrations are above the lower limit of quantification.

Further details regarding descriptive analyses of PK data and population PK modelling will be provided in the SAP.

14.6 Analysis of Safety

Safety will be assessed based on SAEs and non-serious AEs associated with study assessments and/or study conduct. Concomitant medications will also be collected. Complete details of the safety analyses will be provided in the SAP.

14.6.1 Adverse Events

Adverse events associated with study assessments and/or study conduct will be coded using the most up-to-date version of the MedDRA dictionary, and grouped by primary system organ class. These events will be summarised with frequency and percentage, by system organ class and preferred term, for Part A and Part B and overall with separate summaries for all AEs, drug-related AEs, serious AEs and AEs leading to discontinuation of study treatment. The incidence of deaths will also be reported, and the primary cause of death summarised.

14.6.2 Extent of Exposure

This is an observational study with no drug intervention.

14.6.3 Other Safety Variables

The results of scheduled assessments of concomitant medications will be summarised. Further details will be provided in the SAP.

14.7 Interim Analysis

No interim analysis is planned.

14.8 Handling of Missing Data

In general, missing data (caused by premature discontinuation or otherwise) will not be imputed.

14.9 Protocol Deviations

A listing of protocol deviations will be presented by subject using the Full Analysis Set for the complete study period.

15 ETHICS AND RESPONSIBILITIES

15.1 Good Clinical Practice

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

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

15.2 Institutional Review Board

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

15.3 Informed Consent

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

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

The written informed consent process will include the review of oral and written information regarding the purpose, methods, anticipated duration and risks involved in study participation. The Investigator is to ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided. The Investigator or a person designated by the Investigator must also explain to each subject that participation is voluntary, and that consent can be withdrawn at any time and without reason. Subjects will receive a signed and dated copy of the signed ICF before any study-specific procedures are conducted.

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

If the subject is unable to read, an impartial witness must be present during the entire informed consent discussion. After the subject has provided oral consent for the subject to participate in the study, the witness' signature on the written ICF will attest that the informed presented was accurate and understood.

15.4 Records Management

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

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

The minimum retention time for retaining study records will be in accordance with the strictest standard applicable for the study site as determined by local laws, regulations or institutional requirements. At a minimum, records will be maintained for a period of 25 years after the end of the study. If the Investigator withdraws from the study (e.g., relocation, retirement) all study-related records should be transferred, in a written agreement with Indivior, to a mutually agreed upon designee within Indivior-specified timeframe.

16 AUDITING AND MONITORING

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

In accordance with applicable regulations, GCP and Indivior procedures, the clinical monitor(s) will periodically contact the site, which may include conducting on-site visits as per the Clinical Monitoring Plan and the Site Initiation Visit Report.

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

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

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

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centres, review of protocol procedures with the Investigators and associated personnel before the study, periodic monitoring visits by Indivior, and direct transmission of clinical laboratory data from a diagnostic laboratory into Indivior's (or designee's) database. Written instructions will be provided for collection, preparation, and

shipment of blood, plasma and urine samples. Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study. Indivior (or designee) will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to Indivior (or designee). Any discrepancies will be resolved with the Investigator or suitably qualified designee, as appropriate.

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

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

17 AMENDMENTS

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

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

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

18 STUDY REPORTS AND PUBLICATIONS

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.

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

19 STUDY TERMINATION

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

20 CONFIDENTIALITY

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

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

21 REFERENCES

Kampman K, Jarvis M. ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. J Addict Med 2015;9:1–10.

Ohtani M. Basic pharmacology of buprenorphine. Eur J Pain Suppl. 2007 Sep;1(S1):69-73.

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

22 APPENDICES

Appendix 1 – Schedule of Events

	Screening	Part A	END OF PART A	Part B	
Visit		**Visit 1[a]**	**Subjects can proceed into Part B only if they meet continuation criteria[b]**	**Visit 2**	**Visit 3[a]**
Day	**Day 1[c]**	**Day 1[c]**		**30 days from Visit 1**	**30 days from Visit 2**
Visit Window				**±7 days**	**±7 days**
Informed Consent	X				
Demographics	X				
Eligibility Criteria	X				
Body Weight		X			
Height		X			
Body Mass Index (calculated in eCRF)		X			
Medical History[d]		X			
Urine Sample[e]		X		X	X
Urine Pregnancy Test[f]		X		X	X
Blood (PK) Sample		X		X	X
Adverse Events[g]		X		X	X
Concomitant Medications[h]		X		X	X
Buprenorphine Question[i]				X	X

eCRF=electronic case report form; PK=pharmacokinetic

[a] Visit 1 acts as the End of Study visit for Part A and Visit 3 acts as the End of Study visit for Part B. If a subject experiences the onset of a serious adverse event assessed by the Investigator as related to study procedures within a period of 30 days following study completion or withdrawal, and the Investigator will follow the procedures defined in Section 10 and Section 11 for assessing, documenting, and reporting these events.

[b] Subjects who achieve negative results for both buprenorphine and norbuprenorphine quantitative UDS (irrespective of naloxone result) at Visit 1 will conclude their study participation, as will subjects who achieve a positive result for buprenorphine and/or norbuprenorphine and a positive result for naloxone on the quantitative UDS performed at Visit 1. Subjects who achieve a positive result for buprenorphine and/or norbuprenorphine and a negative result for naloxone on the quantitative UDS performed at Visit 1 can continue into Part B of the study if Part B is still open to enrolment.

[c] The Screening visit becomes Visit 1 for subjects eligible to enter Part A (that is, those that are not screen failures).

[d] Medical history since end of previous participation in Phase III SUBLOCADE study.

[e] From the urine sample collected, aliquots will be sent to the bioanalytical laboratory; additional aliquots will be prepared and sent to the diagnostic laboratory; if applicable, the remaining urine will be used for a dipstick pregnancy test.

[f] Urine pregnancy tests will be performed for any woman of childbearing potential (defined as all women who were not surgically sterile or postmenopausal for at least 1 year prior to informed consent). Pregnancy is not exclusionary for enrolment and pregnancy during the study does not lead to discontinuation.

[g] Only adverse events related to study procedures and/or study conduct should be collected in the eCRF.

[h] Concomitant medications are all medications taken during the study, including any prescribed medication-assisted treatment (methadone, naltrexone, buprenorphine) and will be captured. Of note, any extended-release buprenorphine treatment initiation will lead to study discontinuation.

[i] Ask about the subject's illicit buprenorphine use in the last 14 days. If the subject has used prescribed and not illicit buprenorphine, capture in Concomitant Medications. Illicit use will not impact the subject's participation on the study.