STATISTICAL ANALYSIS PLAN: 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

Final Version: 23 Oct 2023

NCT: NCT05704543

STATISTICAL ANALYSIS PLAN
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

Product: SUBLOCADE® (buprenorphine extended-release) injection

Short Title: SUBLOCADE Alternative Injection Locations

Sponsor Name: Indivior Inc.

Legal Registered Address: Indivior Inc., 10710 Midlothian Turnpike, Suite 125, North Chesterfield, VA 23235 USA

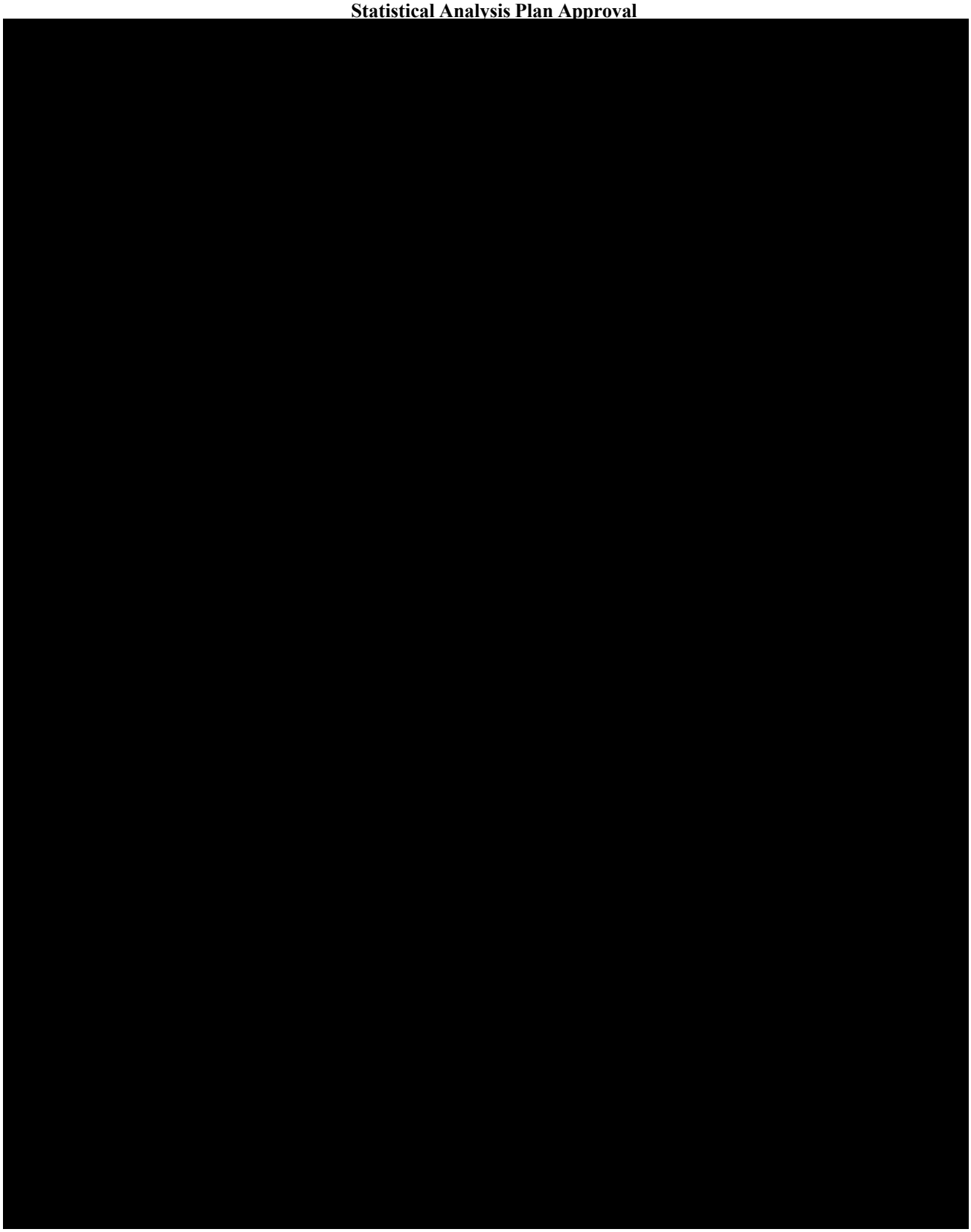
Regulatory Agency Identifier Number(s)

Registry ID: NCT05704543

Registry Name: clinicaltrial.gov

Version: 2.0

Statistical Analysis Plan Approval



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1 INTRODUCTION

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

Having one 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. Therefore, this study will assess the relative bioavailability of buprenorphine (BUP) when SUBLOCADE is administered to these alternate injection sites compared to the currently approved injection location, abdomen in participants with OUD.

1.1 Version History

This Statistical Analysis Plan (SAP) for study INDV-6000-405 is based on the protocol dated 18 Nov. 2022 and eCRF dated 6 Dec. 2022. SAP approval history is shown in Table 1.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study INDV-6000-405. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Table 1. SAP Version History Summary

SAP Version	Associated Protocol Amendment	Approval Date	Change	Rationale
1.0	Not Applicable	23OCT2023	Not Applicable	Original version
2.0	Not Applicable		Changed definition of prior and concomitant medication Added Appendix 8 to illustrate this definition.	To be consistent with the other studies in the portfolio.

1.2 Objectives and Endpoints

Objectives, endpoints and estimands are detailed in Table 2.

Table 2 Objectives, Endpoints and Estimands

Objective Clinical Category	***Statistical Category***	***Estimand***		
		Endpoint	***Population***	***population-level summary***
Primary Objective: To assess the relative bioavailability of buprenorphine (*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.*				
Pharmacokinetic	*Primary*	*$AUC_{0\text{-}28\ Days}$ of BUP plasma concentration*	*PK evaluable*	*Geometric mean ratios with 90% confidence intervals (CIs)*
	Primary	*C_{max} of BUP plasma concentration*	*PK evaluable*	*Geometric mean ratios with 90% CIs*
Secondary Objective: To evaluate the safety and tolerability of SUBLOCADE when administered at alternative injection locations, in comparison to the abdomen				
AEs	*Secondary*	*Proportion of participants with treatment-emergent adverse events (TEAEs)*	*Safety*	*Categorical descriptive*
	Secondary	*Proportion of participants with TEAEs identified as injection site reactions*	*Safety*	*Categorical descriptive*
	Secondary	*Proportion of participants with treatment-emergent serious adverse events (SAEs)*	*Safety*	*Categorical descriptive*
Injection site assessments	*Secondary*	*Injection site grading at 10 minutes and 2 hours post SUBLOCADE dosing*	*Safety*	*Numeric or categorical descriptive*
	Secondary	*Injection Site Pain VAS at 1, 5, 10, 15 and 30 minutes post SUBLOCADE dosing*	*Safety*	*Numeric descriptive*
Exploratory Objectives: • *To assess other PK parameters 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* • *To assess the relative bioavailability of norbuprenorphine and other norbuprenorphine PK parameters following the single SC injection of SUBLOCADE.*				
Pharmacokinetic	*Exploratory*	*AUC_{last} of BUP plasma concentration*	*PK evaluable*	*Geometric mean ratios with 90% CIs*
	Exploratory	*T_{max} of BUP plasma concentration*	*PK evaluable*	*Medians, ranges, descriptive*
	Exploratory	*C_{trough} of BUP plasma concentration*	*PK evaluable*	*Numeric, descriptive*
	Exploratory	*$AUC_{0\text{-}28\ Days}$ of norbuprenophine plasma concentration*	*PK evaluable*	*Geometric mean ratios with 90% CIs*
	Exploratory	*C_{max} of norbuprenophine plasma concentrationfrom*	*PK evaluable*	*Geometric mean ratios with 90% CIs*
	Exploratory	*AUC_{last} of norbuprenophine plasma concentration*	*PK evaluable*	*Geometric mean ratios with 90% CIs*
	Exploratory	*T_{max} of norbuprenophine plasma concentration*	*PK evaluable*	*Medians, ranges, descriptive*
	Exploratory	*C_{trough} of norbuprenophine plasma concentration*	*PK evaluable*	*Numeric, descriptive*

1.3 Study Design

This is a multi-centre, randomized, open-label, single-dose, parallel-group pharmacokinetic study in participants with moderate or severe OUD (based on criteria from the DSM-5).

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 stabilized on 12 mg SUBOXONE® (BUP/naloxone) sublingual film QD for a minimum of 7 days before the SUBLOCADE injection. Dose induction/stabilization onto SUBOXONE film may be completed as outpatient or inpatient, as necessary, according to the prescribing information.

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

Following the residential period (Day -3 to Day -1), on Day 1, eligible participants will be randomized to 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.

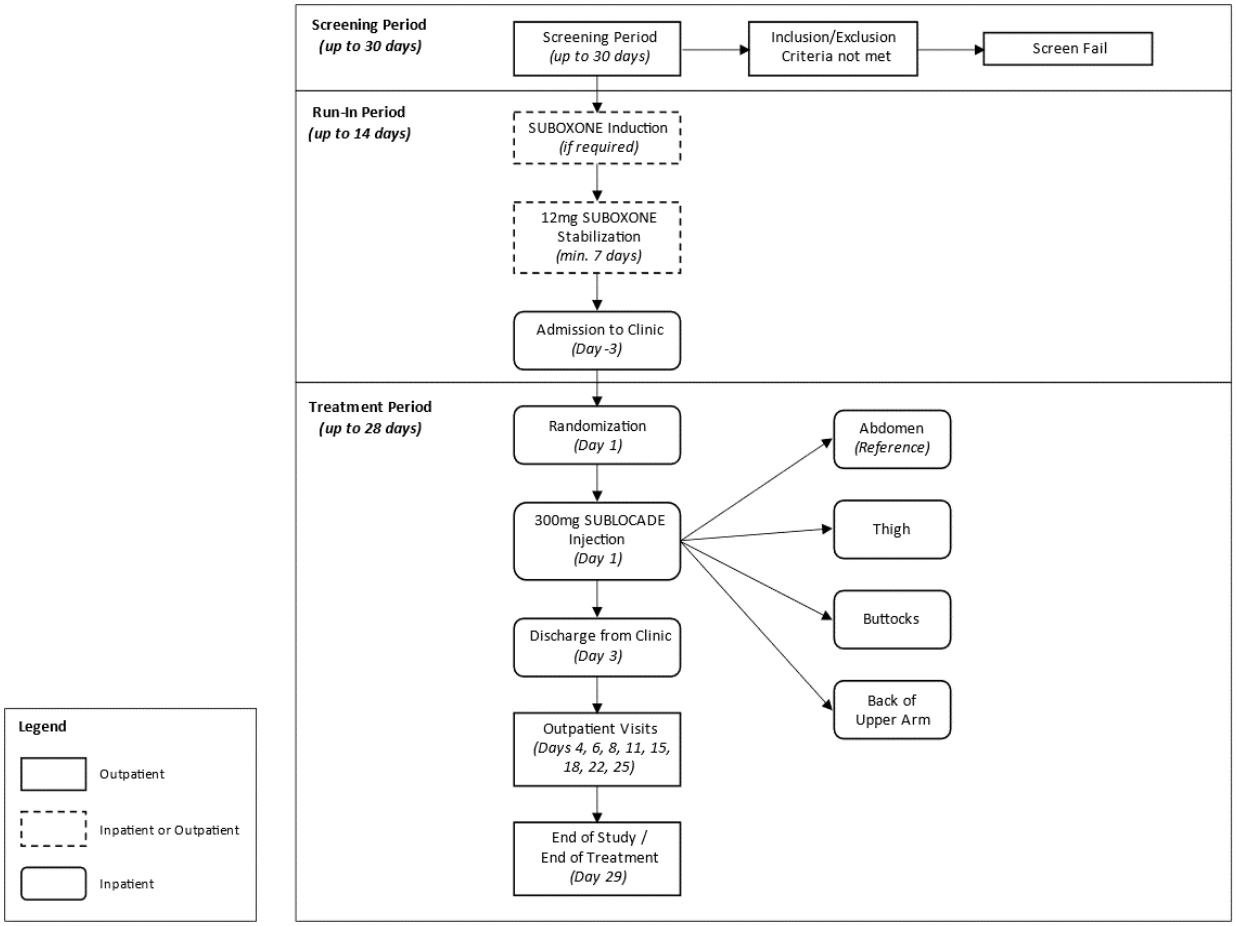
On Day -2, a blood sample will be collected prior to the SUBOXONE dose. On Day -1, blood samples will be collected prior to the SUBOXONE dose, and at 0.5, 1, 2, 4, 6, 12 hours post dose. On Day 1, blood samples will be collected prior to injection of SUBLOCADE, and at 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 hours post dose. Blood samples will also be collected on Days 4, 6, 8, 11, 15, 18, 22, 25 and 29, as close to the time of SUBLOCADE injection performed on Day 1 as possible.

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

Approximately 80 participants in the United States will be randomized 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), Treatment (up to 11 days in the Residential Period and up to 25 days in the Non-residential Period), and Follow up, will be up to approximately 66 days.

The study schematic is illustrated in Figure 1 below.

Figure 1. Study schematic



2 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.

2.1 Multiplicity Adjustment

Not applicable, as there will be no formal hypothesis testing.

3 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 randomized 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 the abdomen (the reference injection location).

4 POPULATIONS FOR ANALYSIS

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database. Classifications will be documented per standard operating procedures.

The analysis populations are defined as shown in Table 3. below.

Table 3. Populations for Analysis

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

5 STATISTICAL ANALYSES

5.1 General Considerations

AUC and C_{max} values will be summarized using descriptive statistics such as the geometric mean and coefficient of variation (CV%). T_{max} values will be summarized as the median, minimum, and maximum. Other continuous variables will be summarised using descriptive statistics such as mean, standard deviations (SD) and/or CV%, median, minimum, and maximum. Categorical variables will be reported as frequency counts (including number missing) and the percentage of participants in corresponding categories.

PK parameters will be derived by noncompartmental analysis with Phoenix™ WinNonlin® software (Version 8.3.4 or higher, Certara, LP)[1] in conjunction with Certara Integral (Version 22.10.1 or higher, Certara, USA, Inc.)[2] using actual sampling times. SAS® software (SAS Institute, Cary, North Carolina)[3] will be used for the statistical analyses and the production of TFLs.

BUP and norbuprenophine plasma concentrations following SUBLOCADE injection will be summarised at each scheduled time point by injection location. The PK profile of each analyte will be summarized graphically by injection site, using both linear and semi-log plots.

Additionally, BUP and norbuprenophine plasma concentrations during the run-in period with SUBOXONE film will also be be summarised at each scheduled time point, and graphically displayed using both linear and semi-log plots.

Spaghetti plots (each individual participant's plasma concentration shown on the same plot, separate plots for each injection site location) will also be generated for both analytes. These plots will include each participant's plasma concentrations during both the inpatient portion of the run-in period and the randomized period. (ie. X-axis will range from Day -2 to Day 29).

5.1.1 Timing of Analyses

Final data analysis will be performed after all BUP and norbuprenorphine PK parameters have been derived, participants belonging to each analysis population (Table 3.) documented and the database locked.

5.1.2 Populations for Analyses

By-timepoint summaries and graphical displays of PK profiles (e.g., buprenorphine plasma concentration) following the SUBLOCADE dose will use the Safety Analysis Set.

PK parameters following the SUBLOCADE dose will be summarized and analysed using the PK evaluable set.

All safety data (eg. TEAEs, injection site grading) following the SUBLOCADE dose will be summarized using the Safety Analysis Set.

By-timepoint summaries and graphical displays of PK profiles (e.g., buprenorphine plasma concentration) during the run-in period will use the Enrolled participant set.

All safety data during the run-in period will be summarized using the Run-In Safety Analysis Set (same as the Enrolled participant set).

5.2 Participant Dispositions

The number and percentage of participants who were screened, enrolled (i.e., received at least 1 dose of SUBOXONE film), randomised and not randomised (including the reason for not randomising), will be summarized by study site and overall, using the number of participants in the screened population as the denominator.

The number and percentage of participants who received SUBLOCADE dose and completed the study, and the number and percentage of participants who belong to the PK Evaluable Set and the safety analysis set (i.e., received SUBLOCADE dose), as well as participants who discontinued early and reason, will be summarized by randomised injection site location and overall, using the number of participants in the randomised population as the denominator. If actual treatment (injection site location) received is different from the randomised treatment for any participant, dispositions will be repeated by the actual injection site location.

5.3 Primary Endpoint(s) Analysis

5.3.1 Definition of endpoint(s)

The primary PK parameters of BUP following SUBLOCADE injection will be derived as shown in Table 4.

Table 4. Primary PK parameters

Parameter	Description
$AUC_{0\text{-}28\ Days}$	Area under the BUP plasma concentration-time curve from time zero (Day 1) to 28 days post-dose (Day 29), calculated by the linear trapezoidal method.
C_{max}	Maximum observed plasma concentration of BUP

5.3.2 Main analytical approach

Estimand strategy: Principal stratum strategy will be used, such that only subjects with an adequate amount of PK data will be included in the analysis.

Analysis set: PK Evaluable Set

Analysis methodology: Natural log-transformed BUP $AUC_{0\text{-}28\ Days}$ and C_{max} from SUBLOCADE Phase will be analyzed using an analysis of variance (ANOVA) model with injection site location as the independent variable. The 90% confidence interval 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 three alternative injection sites (test) versus abdomen (reference; [namely: back of upper arm vs abdomen, buttocks vs abdomen, and thigh vs abdomen])

Intercurrent events and missing data: Missing values will be retained as missing in the analysis.

5.4 Secondary Endpoint(s) Analysis

All secondary endpoints (i.e., safety endpoints) will be based on the Safety Analysis Set. All summaries will be by the actual injection site location and for overall. The difference to

abdomen injection location (with 95% confidence interval) will be estimated for injection locations of upper arm, buttocks, and thigh.

The following secondary endpoints will be derived as the proportion of participants reporting at least one of the specified events, and summarized 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 (CMQ). See Section 6.4 for the complete list of PTs for the CMQ.

Further details on Safety Analysis are detailed in Section 5.6.2.

Each component of the Injection site grading (pain, tenderness and erythema/redness, induration, swelling) at 10 minutes and 2 hours post SUBLOCADE dosing will be summarized using frequency counts and percentages of participants reporting the specific level of severity, including none (Grade 0), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or potentially life threatening (Grade 4) as continuous score (0 to 4). The assessments will be tabulated according to nominal time points, with/without excluding the assessments at time points out of the assessment windows (Protocol 10.6 Appendix 6 Table 11).

Injection Site Pain Visual Analog Scale (VAS) at 1, 5, 10, 15 and 30 minutes post SUBLOCADE dosing will be summarized using descriptive statistics. The assessments will be tabulated according to nominal time points, with/without excluding the assessments at time points out of the assessment windows.

5.5 Tertiary/Exploratory Endpoint(s) Analysis

The following PK parameters for SUBLOCADE will be derived as shown in Table 5. for BUP and Table 6. for norbuprenorphine. 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 plasma terminal half-life reported for SUBLOCADE (43-60 days).

Table 5. Additional PK Parameters of BUP Following SUBLOCADE Injection

Parameter	Description
AUC_{last}	Area under the BUP plasma concentration-time curve from time 0 (Day 1) 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}	BUP plasma concentration measured on Day 29

Table 6. **PK Parameters of Norbuprenorphine Following SUBLOCADE Injection**

Parameter	Description
$AUC_{0\text{-}28\ Days}$	Area under the norbuprenorphine plasma concentration-time curve from time zero (Day 1) to 28 days post dose (Day 29), calculated by the linear trapezoidal method
AUC_{last}	Area under the norbuprenorphine plasma concentration-time curve from time 0 (Day 1) to the last quantifiable concentration, 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}	Norbuprenorphine plasma concentration measured on Day 29

AUC_{last} for both analytes, and $AUC_{0\text{-}28\ Days}$ and C_{max} for norbuprenorphine will be analyzed using the same statistical model as described in Section 5.3.2.

5.6 Other Safety Analyses

5.6.1 Extent of Exposure

Regarding the exposure to SUBOXONE in the Run-in Period, the following will be summarized for the Run-In safety and Safety Analyses Sets.

- The number of days of SUBOXONE use prior to randomization. The number of days will be calculated as the date of the last dose of SUBOXONE minus the date of the first dose of SUBOXONE plus 1.
- The total SUBOXONE dose and average daily SUBOXONE dose during the entire run-in period, calculated as the total cumulative dose divided by the number of days of use.
- The total SUBOXONE dose and average daily SUBOXONE dose between day -7 and day -1.

5.6.2 Adverse Events

Treament Emergent Adverse Events (TEAEs) are defined as adverse events with a start time that is equal to or later than the initiation of the drug treatment or any event already present that worsens in either intensity or frequency following drug exposure.

TEAEs with start date-time after the date of the 1st SUBOXONE dose and before the date of SUBLOCADE injection will be reported for the run-in period, using run-in safety and Safety Analysis Set.

TEAEs with start date-time equal to or after SUBLOCADE injection will be reported for the post-injection period, using Safety Analysis Set, by actual injection site and overall.

TEAEs will be coded to system organ class (SOC) and preferred term (PT) using MedDRA. Incidence and incidence proportion of TEAE (number and percentage of participants reporting the TEAE at least once during the run-in period or the post-injection period) and TEAEs identified as injection site reactions (post-injection period only) will be summarised by SOC and PT. Separate summaries will be provided for the two periods for all TEAEs, TEAEs identified as injection site reactions (post-injection period only), Serious TEAEs, drug related TEAEs and TEAEs leading to discontinuation of study treatment (SUBOXONE or SUBLOCADE).

TEAEs will also be summarized by maximum severity and relatedness within SOC and PT. If an AE is reported more than once by a subject within a SOC and/or PT, the maximum reported level of severity/relatedness will be used at each level of summation in the severity/relationship summary tables. Missing severity and relatedness will be queried until resolution. If resolution is not possible, missing severity will be summarized as “severe” and missing relatedness will be summarized as “related.”

5.6.3 Additional safety assessments

5.6.3.1 Laboratory Data

Except for the pregnancy test which is done both at screening and upon admission to the clinical site, all laboratory evaluations (Table 7) at screening will be summarized using both the Run-In safety and the Safety Analysis Set. Liver function tests will be summarized by time point, using Safety Analysis Set. In calculating summary statistics for numeric lab test values, any reported value that include qualifiers (ie, <, ≤, >, ≥) will be summarized as the limit of quantification. E.g. > 9 will be summarized as 9.

Pregnancy test results will only be listed.

Table 7. Laboratory Assessments

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	Blood urea nitrogen (BUN) Potassium Creatinine Sodium Calcium	Bicarbonate Chloride Glucose (fasting or non-fasting) Creatine phosphokinase (CPK)
Liver Function Test	Albumin Lactate dehydrogenase (LDH) Total protein Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (ALP) Gamma glutamyl transferase (GGT) Total and direct bilirubin	
Pregnancy Testing	Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)	
Urine Drug Screen	Opioids Cocaine Fentanyl 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) *If a central laboratory is being utilised and protocol-required additional local laboratory assessments are needed, include the last bullet in the Other screening tests section of the table ([All study required laboratory…):*
Urinalysis (Categorical)	Specimen Appearance, Bilirubin, Color, Glucose, Ketone, Leucocyte Esterase, Nitrite, Occult Blood, Protein, Urobilinogen, Erythrocytes, Leukocytes
Urinalysis (Continuous)	pH, Specific Gravity.

5.6.3.2 Vital signs

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate) will be summarized by time point, using the Safety Analysis Set and Run-In Safety Set.

5.6.3.3 ECG data

ECG interpretation (normal, abnormal but not clinically significant, abnormal and clinically significant) will be summarized by time point. Numeric 12-lead ECG parameters [heart rate, PR interval, QRS duration, QT interval, Fridericia's corrected QT interval (QTcF)] will also be summarized. All summaries will be based on the Safety Analysis Set and Run-In Safety Set.

5.7 Other Analyses

5.7.1 Major Protocol Deviations

Major protocol deviations will be identified and documented prior to database lock and will be summarized by category (eg, prohibited medication, out-of-window assessment), per the Protocol Deviation Plan for the study, for screened subjects. Deviations that occur in subjects who were randomized and not randomized will be summarized separately. All major protocol deviations will be listed.

5.7.2 Demographic and Baseline Disease Characteristics

Demographic and other baseline characteristics will be summarized separately for the run-in safety set, safety set and PK Evaluable Set, if different. Parameters to be summarized will be age, sex, race, ethnicity, fertility status, and height/weight/body mass index, drug use history and route of administration.

5.7.3 Medical and Psychiatric History

Relevant medical history will be coded using MedDRA and will be summarized for the Run-In Safety population and safety population (PK population, if different).

5.7.4 Urine Drug Screen Results

The number and percentage of participants with positive UDS will be summarized by time point, using the Run-In safety analysis set and Safety Analysis Set. The denominator of the percentage is the number of participants with available results for the individual drug. The opioids (overall) will include opiates/morphine, methadone, oxycodone, and fentanyl. If any of these are "Positive", then opioids (overall) will be defined as "Positive". If all non-missing test results are negative, then opioids (overall) will be defined as "Negative". Amphetamine and methamphetamine will be combined into one class as amphetamine/methamphetamine, using the similar definition for "Positive/Negative" as opioids (overall).

5.7.5 Prior and Concomitant Therapies and Medications

Therapies and medications will be collected from screening through EOS and will be coded using Anatomical Therapeutic Chemical (ATC) classification codes via the World Health Organization Drug Dictionary (WHO-DD). Prior and concomitant medications during run-in/post-injection period are defined in Appendix 8: Concomitant Medication Definition.

Prior and concomitant medications will be summarized using the run-in safety and safety populations. Concomitant medications during the run-in and post-injection periods will be summarized separately using the run-in safety and safety populations, respectively. The summary of incidence (number and percentage of subjects reporting the medication at least once) will be sorted alphabetically by therapeutic class (ATC level 3) and standardized medication name.

5.7.6 Subgroup analyses

In order to understand the study site-to-site variation in injection technique and assessment of injection site reactions, injection site grading and injection site pain VAS summary tables will be repeated for each study site.

5.8 Interim Analyses

Not applicable.

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1: List of Abbreviations

Table 8. List of Abbreviations

Abbreviation	Definition
AE	adverse event
ANOVA	Analysis of variance
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
BLQ	below the limit of quantitation
BP	blood pressure

Table 8. List of Abbreviations

Abbreviation	Definition
BUP	buprenophine
CI	confidence interval
C_{max}	maximum observed concentration
CMQ	customised MedDRA queries
CSR	clinical study report
ECG	electrocardiogram
ICF	Informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
PT	preferred term
QT	QT
QTcF	corrected QT (Fridericia method)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event

6.2 Appendix 2: Changes to Protocol-Planned Analyses

Not applicable.

6.3 Appendix 3: Definition and Use of Visit Windows in Reporting

Regardless of any actual blood draw time deviations from the scheduled time, summary statistics by time point (for data tabulations and figures) will use the scheduled time point.

6.4 Appendix 4: Endpoint Derivations

6.4.1 PK Parameters

Plasma PK parameters will be calculated by non-compartmental analysis using WinNonlin software for BUP and norbuprenorphine. Actual sampling times will be used in the calculations.

If quantifiable data are not available through 28 days (T_{last} <28 days), the following rules will be used to extrapolate $AUC_{0\text{-}28\ Days}$ from AUC_{last} via linear regression through the terminal log-linear segment of the plasma concentration-time curve:

- At least three quantifiable concentrations will be used in the regression
- C_{max} or data prior to C_{max} will not be included in the regression.
- The adjusted regression coefficient (R^2 adj) should be ≥ 0.80.

6.4.2 Handling of BLQ and abberant plasma concentrations

Plasma concentrations that are below the lower limit of quantification (BLQ) will be treated as zero for the time point summary statistics and linear-scale plots of concentrations and excluded from semi-logarithmic-scale plots of concentrations.

For deriving BUP and norbuprenorphine PK parameters, all plasma concentrations that are BLQ prior to the peak plasma concentration (C_{max}) will be set to zero. Post C_{max}, BLQ values will be handled as follows:

- Embedded BLQ values that are between two measurable concentrations will be set to missing

- Measurable concentrations between two BLQ values will be set to missing

- If two or more consecutive BLQ concentrations are followed by quantifiable concentrations, these quantified values will be set to missing

- If a BLQ concentration is followed by a quantifiable concentration, and the quantifiable concentration is then followed by two or more consecutive BLQ concentrations, the quantifiable concentration will be set to missing

- Terminal BLQ values following the last quantifiable time point will be set to missing

- No concentration estimates will be imputed for missing sample values.

6.4.3 Injection site Reactions Customised MedDRA Queries (CMQ)

The PTs used to categorize the injection site reactions are shown in **Table 9** below.

Table 9 CMQ List of Preferred Terms for Injection Site Reactions

Preferred Term	**Preferred Term**
Immediate post-injection reaction	Injection site ulcer
Injection related reaction	Injection site urticaria
Injection site abscess	Injection site vesicles
Injection site cellulitis	Injection site warmth
Injection site infection	Injection site ischaemia
Injection site pustule	Injection site coldness
Injection site abscess sterile	Injection site discolouration
Injection site anaesthesia	Injection site photosensitivity reaction
Injection site atrophy	Injection site swelling
Injection site bruising	Injection site discomfort
Injection site cyst	Injection site calcification
Injection site dermatitis	Injection site movement impairment
Injection site erosion	Injection site lymphadenopathy
Injection site erythema	Injection site nodule
Injection site extravasation	Embolia cutis medicamentosa
Injection site fibrosis	Injection site scar
Injection site granuloma	Injection site discharge
Injection site haematoma	Injection site pallor
Injection site haemorrhage	Injection site papule
Injection site hypersensitivity	Injection site injury
Injection site hypertrophy	Injection site scab
Injection site induration	Injection site eczema

Injection site inflammation	Injection site streaking
Injection site irritation	Injection site dryness
Injection site mass	Injection site laceration
Injection site necrosis	Injection site macule
Injection site nerve damage	Injection site vasculitis
Injection site oedema	Injection site exfoliation
Injection site pain	Injection site dysaesthesia
Injection site paraesthesia	Injection site plaque
Injection site phlebitis	Injection site hyperaesthesia
Injection site pruritus	Injection site hypoaesthesia
Injection site rash	Injection site hypertrichosis
Injection site reaction	Injection site thrombosis

6.5 Appendix 5: Methods to Manage Missing Data

6.5.1 Adverse event data

Missing AE Severity

In the unlikely event that resolution is not possible, missing severity will be imputed as “severe” in summaries.

Missing AE Relationship to Study Drug

In the unlikely event that resolution is not possible, missing relationship will be imputed as “related” in summaries.

Missing Date Information for Adverse Events

- Missing day and month
  - If the year is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.
  - If the year is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.
  - If the year is after the year of the date of the first dose of investigational product, then January 1 will be assigned to the missing fields.
- Missing month only
  - The day will be treated as missing and both month and day will be replaced according to the above procedure.
- Missing day only

- If the month and year are the same as the month and year of the date of the first dose of investigational product, then the day of the first dose of investigational product will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.
- If the stop date is after the date of the first dose of investigational product, the date of the first dose of investigational product will be assigned to the missing start date.
- If the stop date is before the date of the first dose of investigational product, the stop date will be assigned to the missing start date.

6.5.2 Missing Date Information for Concomitant Medications

- Missing day and month
  - If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose will be assigned to the missing fields.
  - If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.
  - If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then January 1 will be assigned to the missing fields.

- Missing month only
  - The day will be treated as missing and both month and day will be replaced according to the above procedure.

- Missing day only
  - If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the first dose will be assigned to the missing day.
  - If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day.
  - If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

- Incomplete Stop Date
  - For deriving concomitant medication flag, the following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, impute it as descripted in Section 17.4. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

- Missing day and month
  - If the year of the incomplete stop date is the same as the year of the date of the last dose of investigational product, then the day and month of the date of the last dose will be assigned to the missing fields.
  - If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then December 31 will be assigned to the missing fields.
  - If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then January 1 will be assigned to the missing fields.

- Missing month only
  - The day will be treated as missing and both month and day will be replaced according to the above procedure.

- Missing day only
  - If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the last dose will be assigned to the missing day.
  - If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day.
  - If either the year is after the year of the date of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

6.6 Appendix 6: Methods to Manage Character Values of Clinical Laboratory Parameters

Reported values of clinical laboratory parameters that include qualifiers (ie, <, ≤, >, ≥) will be listed as reported but will be summarized without the qualifier.

6.7 Appendix 7: Data Set Descriptions

Trial data sets will consist of CRF exports and external data files. External files may be used for PK parameters, protocol deviations and data from the central laboratory, for example.

6.8 Appendix 8: Concomitant Medication Definition

The definition of prior and concomitant medications is illustrated below. Two timing flags will be derived based on the tables below.

Table 10 Definition of Prior and Concomitant Medications for Run-In Period

End Date of Non-Study Medication	Start Date of Non-Study Medication		
	Missing	< Start date of SUBOXONE	≥ Start date of SUBOXONE and ≤ end date of SUBOXONE
Missing (includes flagged as "Ongoing")	Prior Concomitant (Run-In)	Prior Concomitant (Run-In)	Concomitant (Run-In)
< Start date of SUBOXONE	Prior	Prior	Data Error
≥ Start date of SUBOXONE and ≤ end date of SUBOXONE	Prior Concomitant (Run-In)	Prior Concomitant (Run-In)	Concomitant (Run-In)

If a medication's end date is on or after the date of SUBLOCADE injection, then it will be classified as concomitant Post-Injection as shown in Table 11.

Table 11 Definition of Concomitant Medications for Post Injection Period

End Date of Non-Study Medication	Start Date of Non-Study Medication		
	Missing	< SUBLOCADE injection date	≥ SUBLOCADE injection date
Missing (includes flagged as "Ongoing")	Concomitant (Post-Injection)	Concomitant (Post-Injection)	Concomitant (Post-Injection)
≥ SUBLOCADE injection date	Concomitant (Post-Injection)	Concomitant (Post-Injection)	Concomitant (Post-Injection)

Prior medications will be defined using the first table only. A medication is considered concomitant if it is concomitant either during run-in period or during post-injection period.

7 REFERENCES

1. Phoenix™ WinNonlin® (Version 8.3.4.295 or higher, Certara, LP.)
2. Certara Integral (Version 22.10.1, Certara, USA, Inc.)
3. SAS Institute Inc., Cary, NC, 27513, USA