Statistical Analysis Plan

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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

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STATISTICAL ANALYSIS PLAN

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1. TITLE PAGE

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

Version 1 (22 May 2019)

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CRF	Case Report Form
EPRED	Monte Carlo-generated population predictions
EWRES	Monte Carlo-generated weighted residuals
FAS	Full Analysis Set
IA	Interim Analysis
ICF	Informed Consent Form
IMP	Importance sampling
IPRED	Individual predictions
IWRES	Individual weighted residuals
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NONMEM	Nonlinear mixed-effects modeling
OTC	Over the Counter
PDV	Protocol Deviation
PK	Pharmacokinetic(s)
PT	Preferred Term
SAE	Serious Adverse Event
SAEM	Stochastic approximation expectation-maximization algorithm
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SC	Subcutaneous
SE	Standard Error
SI	International System
SOC	System Organ Class
TFLs	Tables, Listings, and Figures
UDS	Urine Drug Screen
ULN	Upper Limit of Normal
WHODRUG	World Health Organization Drug Dictionary

4. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the final reporting and analyses of data collected for the full study (Protocol INDV-6000-402).

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the study protocol version 4.0 dated 22 Apr 2019 and CRF version 1.0 dated 20 Dec 2018.

This multicenter investigation will enroll 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 subcutaneous (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 urine drug screen (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) apart between the two 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 presented in Figure 1.

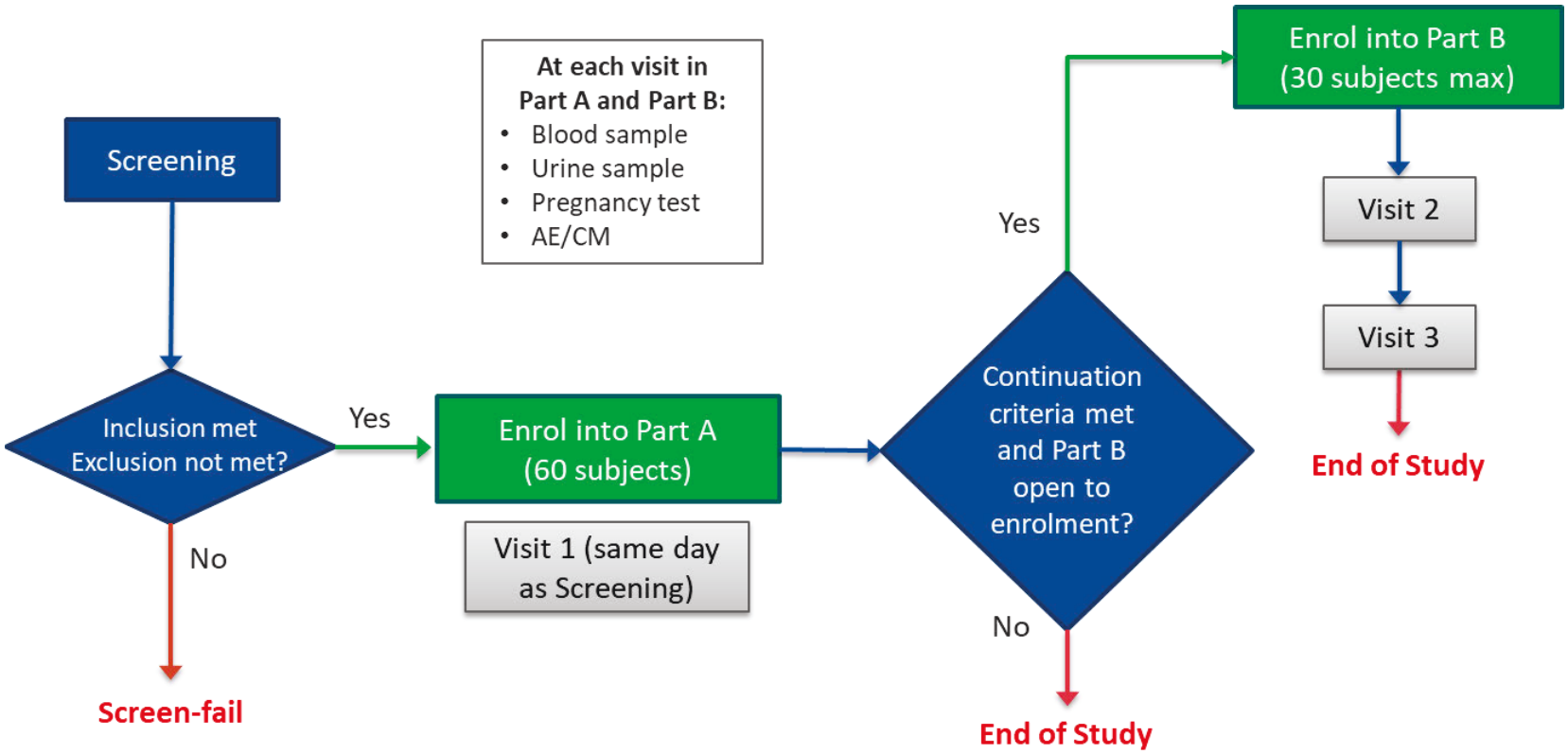


Figure 1 **Study Schematic**

5. STUDY OBJECTIVES

5.1 PRIMARY

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

5.2 EXPLORATORY

The exploratory objectives of this study are the following:

- Refine pharmacokinetic (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

- Assess relationships between drug plasma concentrations, free drug concentrations in urine, and UDS results for buprenorphine from a diagnostic laboratory.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Data will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented. For continuous variables, the number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum will be presented. All data will be presented in listings (including unscheduled visits).

In general, missing data will not be imputed, except for methods for handling missing data specified in Appendix 2.

6.1 SUBJECT POPULATIONS

6.1.1 Screened Population

The Screened Population Set includes any subject who signed the informed consent form.

6.1.2 Safety Analysis Set

Safety Analysis Set Part A: The Safety Analysis Set Part A consists of all subjects who have completed at least one blood or urine sample collection in Part A (from Scheduled or Unscheduled visits).

Safety Analysis Set Part B: The Safety Analysis Set Part B consists of all subjects who have completed at least one blood or urine sample collection in Part B (from Scheduled or Unscheduled visits).

The **Safety Analysis Set** consists of all subjects who are part of the Safety Analysis Set Part A and/or Part B.

6.1.3 Full Analysis Set (FAS)

FAS Part A: The FAS Part A consists of all subjects who are screen success and who have at least one measure of buprenorphine or norbuprenorphine concentration in plasma or at least one measure of buprenorphine or norbuprenorphine concentration in urine (as free drug or from quantitative UDS) or at least one measure for buprenorphine qualitative UDS in Part A (from Scheduled or Unscheduled visits).

FAS Part B: The FAS Part B consists of all subjects who met continuation criteria for Part B and who have at least one measure of buprenorphine or norbuprenorphine concentration in plasma or at least one measure of buprenorphine or norbuprenorphine concentration in urine (as free drug or from quantitative UDS) or at least one measure for buprenorphine qualitative UDS in Part B (from Scheduled or Unscheduled visits).

The **FAS** consists of all subjects who are part of FAS Part A and/or FAS Part B.

6.1.4 Pharmacokinetic Analysis Set

The PK Analysis Set consists of all subjects who are screen success and who have at least one concentration measure for buprenorphine or norbuprenorphine in plasma or urine.

6.2 MULTIPLE COMPARISONS

No statistical tests are performed for this study and thus no multiple comparisons are performed.

6.3 OTHER VARIABLE CATEGORIES TO PRESENT

Sex

- Male
- Female

Age categories

- 18 - 44
- 45 - 64
- ≥ 65

Race

- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or Other Pacific Islander

- White
- Other

Ethnicity

- Hispanic or Latino
- Not Hispanic or Latino

Baseline body mass index (BMI) categories

- Under weight: < 18.5 kg/m^2
- Normal: ≥ 18.5 kg/m^2 and < 25 kg/m^2
- Over weight: ≥ 25 kg/m^2 and < 30 kg/m^2
- Obese: ≥ 30 kg/m^2

6.4 DEFINITION OF STUDY DAY

Study day is the day relative to the date of Visit 1 in Part A.

7. SUBJECT DISPOSITION

The number and percentage of subjects screened and considered as screen failures, if any, will be summarized. A listing of the inclusion/exclusion reasons for screen failures will be provided, if any.

The number and percentage of subjects in populations of Safety Analysis Set Part A, Safety Analysis Set Part B, FAS Part A and FAS Part B together with the number and percentage of subjects who completed Part A and the number of subjects who completed Part B will be summarized. The population in the Safety Analysis Set will be used as denominator to calculate the percentage. A completer for Part A is the subject in the Safety Analysis Set Part A who has completed all plasma and urine sample collections for Visit 1 (Scheduled or Unscheduled) for Part A. A completer for Part B is the subject in the Safety Analysis Set Part B who has completed all plasma and urine sample collections for Visits 2 and 3 (Scheduled or Unscheduled) in Part B. The reasons Part A subjects did not participate in Part B will be summarized.

If a subject completes Part B but does not complete Part A, a footnote will be added to clarify.

8. PROTOCOL DEVIATIONS

A protocol deviation (PDV) is any change, divergence, or departure from the study design or procedures defined in the protocol as per ICH E3 guidelines. Important PDVs are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect subject's rights, safety, or well-being.

A listing of PDVs, classified as important and not important, will be presented by subject using the Safety Analysis Sets. Except for important PDV defined as below, all other deviations are considered as non-important PDV:

- The subject was deemed eligible for the study but did not meet key inclusion criteria as listed below:
  - 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.
  - The subject must be within 12 months to the last day of the 36th months post his or her last SUBLOCADE injection at the time of the Screening visit.
  - The subject did not provide the informed consent prior to the start of any study procedures.
- Subject was deemed eligible for the study but did meet key exclusion criteria as listed below:
  - 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.
  - The subject has taken any buprenorphine (prescribed or illicit) within 3 weeks prior to the Screening visit.
- Part B continuation criteria: The subject did not meet Part B continuation criterion but continued to Part B.

- The subject was not discontinued after reporting use of SUBLOCADE or any other long-acting buprenorphine product during the study as specified in protocol Section 5.5.

9. DEMOGRAPHICS CHARACTERISTICS

Demographic characteristics (sex, ethnicity, race, age [as continuous (Years) and categories of 18 - 44, 45 - 64, ≥65], weight [kg], height[cm] and body mass index [BMI as continuous (kg/m^2) and categories of <18.5 (underweight), ≥18.5-<25 (normal), ≥25-<30 (overweight), ≥30 (obesity)]) will be summarized using descriptive statistics by the cohorts of Part A and Part B within the Safety Analysis Set and the FAS respectively. Qualitative variables (sex, ethnicity, race, age categories, BMI categories) will be summarized using frequency count and percentage, while quantitative variables (age, weight, height, BMI) will be summarized using mean, SD, median, minimum, and maximum. Demographic data will also be listed for all subjects in the Safety Analysis Set; variables will be added to indicate if the subject belongs to Safety Analysis Set Part A, Safety Analysis Set Part B, FAS Part A and FAS Part B.

Per protocol, the Part B subjects should be a subset of Part A subjects. If this is violated, a footnote will be added to specify.

10. MEDICAL HISTORY

Medical history is collected from the end of previous participation in the latest SUBLOCADE study the subject participated in. The medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 or later version available during study and summarized by the number and percentage of subjects in each System Organ Class (SOC), Preferred Term (PT) by the cohorts of Part A and Part B within the Safety Analysis Set. Subjects will be counted only once for each PT, only once at the System Organ Class (SOC), and only once at subject level for the counting of total number of subjects with a medical history term. Counts will be presented in descending frequency unless otherwise specified.

Medical history data will also be listed for all subjects in the Safety Analysis Set; variables will be added to indicate if the subject belongs to Safety Analysis Set Part A, Safety Analysis Set Part B, FAS Part A and FAS Part B.

11. PRIOR AND CONCOMITANT MEDICATIONS

Based on the study protocol, prior medications are not collected in the study.

Concomitant medications are all medications taken during the study (from first visit to the last visit in the study), including any prescribed medication-assisted treatment (methadone, naltrexone, buprenorphine), and will be captured. Of note, treatment initiation with any extended-release buprenorphine product will lead to study discontinuation.

Concomitant medications will be categorized by preferred term and drug category class, such as ATC classes 1, and/or 2 or 3, per World Health Organization Drug Dictionary [WHODRUG]), Concomitant medications will be summarized by the cohorts of Part A and Part B within the Safety Analysis Set. The number and percentage of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication. For a selected ATC class (for example, ATC Class 2), if the medication is not coded for that class, the value of "Unassigned" will be used in summary table and the "Unassigned" category is always presented in the last in the summary table.

The listing of concomitant medications will be provided for all subjects in the Safety Analysis Set. Variables will be added to indicate if the subject belongs to the Safety Analysis Set Part A, Safety Analysis Set Part B, FAS Part A and FAS Part B. A variable in the listing will indicate whether the medication was also a prior medication (start date prior to the date of Visit 1 in Part A).

12. SAFETY ANALYSES

12.1 ADVERSE EVENTS

Only adverse events (AEs) associated with study assessments and/or study conduct will be collected using the Adverse Event eCRF. If any of these AEs become serious AEs (SAEs), they will be reported to Indivior via the Safety Information Collection Form.

Adverse events associated with study assessments and/or study conduct (AE onsets on or after the first visit in this study) will be coded using the most up-to-date version of the MedDRA dictionary, and grouped by primary SOC. These events will be summarized with frequency and percentage, by SOC and PT, by the cohorts of Part A and Part B within the Safety Analysis Set, with separate summaries for all AEs, AEs related to study procedures (such as urine collection procedure or blood collection procedure), and serious AEs. The incidence of deaths will also be reported.

Since there is no study drug for this study, no treatment emergent AE is defined for this study.

A summary of AEs will be presented by the cohorts of Part A and Part B within the Safety Analysis Set, including the number and percentage of subjects reporting at least one AE, the number and percentage of subjects with the following:

- AE summary
- All AEs by SOC and PT
- All AEs by SOC, PT and severity
- SAEs
- SAEs by SOC, PT and severity

A breakdown of the number and percentage of subjects reporting each AE categorized by SOC and PT coded per the MedDRA dictionary version or later version available during study will be presented by the cohorts of Part A and Part B within the Safety Analysis Set. Note that counting will be by subject not by event, and subjects will be only counted once within each SOC or PT.

A summary of events reported, categorized by severity, will also be provided by the cohorts of Part A and Part B within the Safety Analysis Set. Subjects with multiple events within a SOC or PT will be counted under the category of their most severe event within that SOC or PT. A further tabulation of severe AE will be presented by SOC and PT.

Additionally, all AEs will be summarized by maximum severity (mild, moderate, or severe).

AE will also be listed for all subjects in the Safety Analysis Set, variables will be added to indicate if the subject belongs to the Safety Analysis Set Part A, Safety Analysis Set Part B, FAS Part A and FAS Part B.

12.1.1 Serious Adverse Events

SAEs will be summarized separately by SOC and PT by the cohorts of Part A and Part B within the Safety Analysis Set.

All SAEs recorded on the CRF will be listed for the Safety Analysis Set.

12.1.2 Deaths

Deaths occurring in the study will also be listed for the Safety Analysis Set.

12.2 CLINICAL LABORATORY PARAMETERS

No laboratory data collected for this study.

12.3 VITAL SIGNS

No vital sign data collected for this study

12.4 OTHER SAFETY VARIABLES

12.4.1 Pregnancy Test

Pregnancy test results collected during the study will be listed for the Safety Analysis Set.

13. PHARMACOKINETIC ANALYSIS

A blood sample will be collected at each visit for the determination of buprenorphine and norbuprenorphine plasma concentrations. A urine sample will also be collected at each visit for the determination of free buprenorphine and free norbuprenorphine concentrations; the realization of a qualitative UDS for opioids, including buprenorphine; a quantitative UDS for buprenorphine, norbuprenorphine and naloxone; and the determination of creatinine concentration.

13.1 DESCRIPTIVE ANALYSIS

The number and percentage of subjects with negative and positive results for buprenorphine on the qualitative UDS will be summarized for FAS Part A at Visit 1 and for FAS Part B across Visits 1, 2 and 3. Qualitative UDS results for opioids other than buprenorphine will be summarized in a similar way.

The number and percentage of subjects with negative results for **both** buprenorphine and norbuprenorphine based on quantitative UDS or free drug concentrations will be summarized for FAS Part A at Visit 1 and for FAS Part B across Visits 1, 2 and 3. Negative and positive results for each analyte will also be summarized (buprenorphine, norbuprenorphine and naloxone for quantitative UDS; buprenorphine and norbuprenorphine for free drug concentrations). A negative result will be any concentration below the lower limit of quantification (LLOQ). A positive result will be any quantifiable concentration.

As for urine, the number and percentage of subjects with negative results for **both** buprenorphine and norbuprenorphine concentrations in plasma will be summarized for FAS Part A at Visit 1 and for FAS Part B across Visits 1, 2 and 3. Negative and positive results for each analyte (buprenorphine, norbuprenorphine) will also be summarized. A negative result will be any concentration below the LLOQ. A positive result will be any quantifiable concentration.

For all above tables, missing data will not be imputed. For Visits 2 and 3, data associated with the reported use of illicit buprenorphine at the visit or the use of prescribed buprenorphine within 3 weeks of the assessment will be excluded from all the above summary statistics calculation for that visit only. Those excluded data, if any, will be indicated in the listings. With respect to Visit 1, no data should be excluded since meeting the exclusion criteria infers that there was no use of prescribed or illicit opioid use within 3 weeks prior to the Screening visit.

For the following descriptive analyses, the PK analysis set will be used. A graphical representation of buprenorphine and norbuprenorphine plasma/urine concentrations over time will be provided. Individual plasma/urine concentration-time data will be plotted using the time elapsed from the last SUBLOCADE dose. A solid line will be used to link concentrations from a same subject. 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 (Appendix 4). The purpose of the correction by creatinine urine concentration is to correct for urinary dilution.

For plasma and urine (uncorrected) concentration-time plots, concentrations below the LLOQ will be imputed with the LLOQ value. Three symbols will be used for 1) quantifiable concentrations, 2) concentrations below the LLOQ and 3) quantifiable concentrations associated with the reported use of illicit buprenorphine at the visit or the use of prescribed buprenorphine within 3 weeks of the visit. For concentration-time plots representing buprenorphine or norbuprenorphine urine concentrations after correction with creatinine concentration in urine, concentrations below the LLOQ will not be imputed and will not be shown on the plots.

Norbuprenorphine-to-buprenorphine ratios will be calculated from quantifiable concentrations in plasma, quantifiable concentrations of free drug in urine, and quantifiable concentrations from quantitative UDS. Values will be reported in listings. Summary statistics (mean, SD, median, 5^{th} and 95^{th} percentiles, minimum, maximum) will be calculated by subgroups defined by the intake (yes/no) of prescribed or illicit buprenorphine. One subject may contribute to multiple observations (up to 3).

Relationships between plasma and urine drug concentrations measured on the same day will also be explored by calculating urine-to-plasma ratios for quantifiable concentrations of buprenorphine or norbuprenorphine. Urine drug concentrations corrected by creatinine concentration or uncorrected will both be used to derive those urine-to-plasma concentration ratios. Values will be reported in listings. Summary statistics (mean, SD, median, 5^{th} and 95^{th} percentiles, minimum, maximum) will be calculated by subgroups defined by the intake (yes/no) of prescribed or illicit buprenorphine. One subject may contribute to multiple observations (up to 3).

Finally, plots will be constructed to assess the consistency of norbuprenorphine-to-buprenorphine ratios and of urine-to-plasma concentration ratios over time, using the time elapsed from the last SUBLOCADE dose. A solid line will be used to link data from a

same subject. Different symbols will be used by subgroups defined by the intake (yes/no) of prescribed or illicit buprenorphine.

Equations for correction of buprenorphine or norbuprenorphine urine concentrations or urine-to-plasma concentration ratios with creatinine concentration in urine are presented in Appendix 4.

13.2 POPULATION PHARMACOKINETIC MODELING

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) (modeling report, IND-6000-M05). The purpose is to characterize the long-term decrease in buprenorphine plasma concentration following discontinuation of SUBLOCADE treatment.

The final model will be used to derive population predictions for the 2 dosing regimens of SUBLOCADE and to derive endpoints such as the distribution of times for which buprenorphine plasma concentrations are above the lower limit of quantification.

13.2.1 Existing Population Pharmacokinetic Model for SUBLOCADE

The PK of buprenorphine following repeated SC injections of SUBLOCADE has been well characterized using non-linear mixed effects modeling with the combined analysis of 3 clinical studies: RB-US-12-0005 (Phase IIA multiple-ascending-dose study), RB-US-13-0001 (Phase III pivotal efficacy study) and RB-US-13-0003 (Phase III long-term safety and tolerability study). All studies were conducted in subjects with opioid use disorder following induction and dose stabilization with sublingual buprenorphine tablet or film.

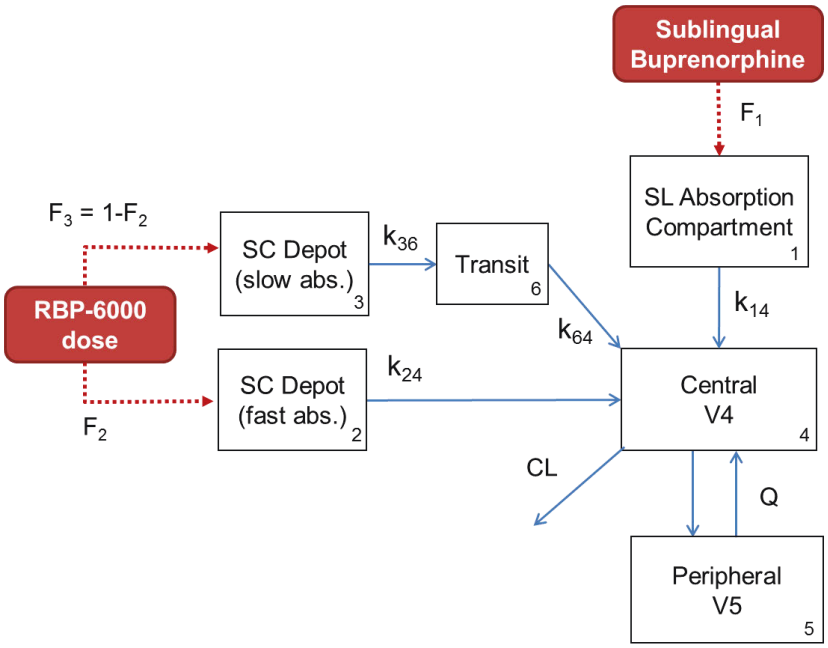
As shown in Figure 2, the disposition model consisted of a 2-compartment model with first-order elimination. The absorption of buprenorphine from the SC injection site was described by a dual absorption model including (i) a first-order absorption rate constant (k24) to characterize the rapid absorption process associated with the early peak, and (ii) a transit compartment absorption model (rate constants k36 and k64) to mimic the slow delivery of buprenorphine from the SC depot. The fraction of SUBLOCADE absorbed via the slow (F3) or fast (F2) process was estimated.

A first-order rate constant (k14) was selected to model the absorption of SL buprenorphine. The relative bioavailability of SUBUTEX (used in Study RB-US-12-0005) vs. SUBLOCADE (F1) was estimated. Changes in bioavailability and absorption rate for

SUBOXONE film (used in Phase III studies) relative to SUBUTEX tablet were also estimated.

The model was parameterized in terms of clearances and volumes. Based on prior knowledge and for mechanistic reasons, clearances and volumes of distribution were allometrically scaled by body weight using the well-established power model and exponents of 0.75 for clearances and 1 for volumes.

Figure 2 **Structural Model for Buprenorphine After Sublingual and Subcutaneous Administration from the Combined Population Pharmacokinetic Analysis of Studies RB-US-12-0005, RB-US-13-0001 and RB-US-13-0003**



See Table 1 for the definition of PK parameters

Source: INDV-6000-M04 Figure 1

The population PK model was developed in 2 steps using NONMEM software version 7.3.0:

- Step 1: Development of base and final covariate models from the joint analysis of Studies RB-US-12-0005 and RB-US-13-0001 (total of 17 235 observations in 507 subjects)

- Step 2: Prediction of Study RB-US-13-0003 and model refinement using the totality of the data (total of 19 686 observations in 570 subjects).

Additional information on model building, model parameter estimates and model evaluation can be found in the PK modeling reports INDV-6000-M04 (Step 1) and INDV-6000-M05 (Step 2).

Overall, the model provided a very good description of the plasma concentration-time profiles following SC injection of SUBLOCADE at each dose level, across the 3 studies. Two statistically significant covariates were identified during the covariate analysis: BMI and sex. Sex had a significant effect on the slow absorption of buprenorphine from the SC depot (k36) but this effect was marginal. Body mass index was also found to affect SC absorption (k24) and the apparent clearance of buprenorphine, with higher buprenorphine peak levels in subjects with a lower BMI.

Model parameter estimates are displayed in Table 1.

Table 1 Estimates of Previous Population Pharmacokinetic Model (Combined Analysis of Phase II/III Data)

Parameter	Description	Estimate (RSE%)		Variance (RSE%)		IIV (%)
k14	Sublingual absorption rate constant (h^{-1})	1.17	(FIXED)	0.190	(FIXED)	45.7
k24	Fast absorption rate constant from SC depot (h^{-1})	0.0276	(5.1)	0.654	(16)	96.1
k36	Slow absorption rate constant from SC depot (h^{-1})	0.00362	(7.4)	1.54	(11)	191
k64	Rate constant from Transit compartment to Central (h^{-1})	0.000510	(3.7)	0.432	(11)	73.5
CL	SUBLOCADE apparent elimination clearance (L/h)	52.0	(1.5)	0.0871	(9.5)	30.2
V4	SUBLOCADE apparent volume of central compartment (L)	433	(27)	0.647	(12)	95.4
Q	SUBLOCADE apparent distribution clearance (L/h)	79.5	(FIXED)	0.334	(FIXED)	63.0
V5	SUBLOCADE apparent volume of peripheral compartment (L)	1110	(FIXED)	0.941	(FIXED)	125
F1	Relative bioavailability of SUBUTEX compared to SUBLOCADE	0.185	(FIXED)	0.195	(FIXED)	46.4
F2	Fraction of SUBLOCADE dose absorbed by fast process	0.0679	(2.2)	0.204	(11)	NA[#]
FRK14	Relative change in k14 for SUBUXONE compared to SUBUTEX	0.650	(11)	NA		NA
FRF1	Relative change in F1 for SUBUXONE compared to SUBUTEX	1.47	(3.5)	NA		NA
F1DOSE	Relative change in F1 for dose ≥ 16mg compared to dose < 16mg	0.765	(FIXED)	NA		NA
θ_{BMI} (CL)	Power coefficient for BMI on CL/F	-0.364	(21)	NA		NA
θ_{BMI} (k24)	Power coefficient for BMI on k24	-1.32	(14)	NA		NA
θ_{SEX} (k36)	Fractional increase in k36 for females	0.0313	(282)	NA		NA
Add	Additive residual error (ng/mL)	0.0373	(14)	NA		NA
Prop	Proportional residual error	0.190	(0.66)	NA		NA

IIV=interindividual variability calculated as $100 \times \sqrt{\exp(\omega^2) - 1}$, where ω^2 is the variance of related subject-specific random effect; NA=not applicable; RSE=relative standard error; # logit-normal distribution.
Source: INDV-6000-M05 Table 5

13.2.2 Dataset Preparation

Buprenorphine plasma concentration data collected in Parts A and B will be merged with the previous NONMEM dataset that was used to develop the population model presented in Section 13.2.1.

R software version 3.4.3 or older will be used for data inspection and for the preparation of the input datafile for the population PK analysis in NONMEM. This will involve obtaining the required study variables from the primary data source for the current and previous studies, calculating the elapsed time from the last SUBLOCADE dose in Study RB-US-13-0003 or Study INDV-6000-301, and merging with the previous dataset combining Phase II/III data. All R codes related to data preparation, identification of potential outliers, and exploratory graphical analysis will be adequately commented for ease of use.

The NONMEM input file will be formatted as a comma separated (.csv) file and will include the following information: subject unique identification number, dosing information, actual sampling times, measured buprenorphine plasma concentrations, demographics (e.g., sex, age, weight, body mass index [BMI], race), study identification number, and flags for potential outliers and concentrations below the LLOQ.

Plasma concentrations below the LLOQ in the current study will be included in the analysis and will be handled using appropriate likelihood-based methodology.

Plasma concentrations associated with the reported use of illicit buprenorphine at the visit or the use of prescribed buprenorphine within 3 weeks of the visit (Part B – Visits 2 and 3) will be flagged as outliers, and although listed in the NONMEM dataset, will not be used for the population PK analysis.

13.2.3 Handling of Outliers

An outlier is defined as an aberrant observation that significantly deviates from the rest of the observations in a particular individual and does not refer to a subject as an outlier. The proportion of outliers in a dataset should be low and such points might be excluded from the analysis given the potential for these observations to impact the convergence and/or parameter estimates (i.e., which may cause a bias) (FDA Guidance, February 1999).

Outlier detection will be based on the visual inspection of individual and pooled data profiles and based on documented information such as the reported use of buprenorphine at the visit or the use of illicit or prescribed buprenorphine prior to the visit.

13.2.4 Population Pharmacokinetic Modeling

The criteria used in selecting the most appropriate models will be based on individual goodness-of-fit plots (e.g., DV vs. IPRED, IWRES vs. IPRED), overall goodness-of-fit plots (e.g., DV vs. EPRED, EWRES vs. EPRED), change in objective function value (likelihood ratio test for nested models) and precision of parameter estimates.

13.2.4.1 Structural model

The structural model selected for the combined analysis of Phase II/III data (Figure 2) will be used in the present analysis. This model assumes that the slow release of buprenorphine from the SC depot can be adequately described by a transit compartment absorption model with first-order rate constants k36 and k64. This model might be revised depending on goodness-of-fit plots for long-term exposure buprenorphine data in the current study.

13.2.4.2 Stochastic model

Individual PK parameters will be assumed to be log-normally distributed, except for the fraction of SC dose allocated to the fast absorption process for which a logit-normal distribution will be used. A combined proportional and additive error structure will be evaluated for the residual error. Alternate error models may be tested if this model is not considered adequate based on the inspection of individual weighted residuals.

13.2.4.3 Covariate analysis

Covariate effects will be implemented as coded in the previous model (Table 1). No additional covariate analysis will be conducted.

13.2.5 Model evaluation

Model evaluation will be performed using visual predictive checks and standard goodness-of-fit plots (including DV vs. IPRED and DV vs. EPRED plots, EWRES vs EPRED and IWRES vs. IPRED plots).

13.2.6 Simulations

Simulations will be conducted using the final model to predict long-term buprenorphine plasma exposure after stopping SUBLOCADE treatment (6 injections of 300 mg or 2 injections of 300 mg followed by 4 injections of 100 mg).

The distribution of predicted buprenorphine plasma concentrations will be summarized at each month over at least 36 months post last SUBLOCADE injection in the simulation

study. The percentage of subjects predicted to fall below the limit of quantification will be calculated at each month. Also, the distribution of times during which buprenorphine plasma concentrations stay above the lower limit of quantification following the last dose of SUBLOCADE will be provided.

Additional simulation studies may be conducted as needed.

14. INTERIM ANALYSIS

No formal interim analysis is pre-specified for the study. However, during the course of the study, data relevant to PK analysis will be summarized and reviewed to facilitate decision making regarding potential modification of study duration.

15. DETERMINATION OF SAMPLE SIZE

The sample size is based on practical considerations and no statistical power is calculated. Approximately 60 subjects will be enrolled 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 enrolled 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.

16. COMPUTER METHODS

Statistical analyses will be performed using version 9.4 (or newer) of SAS on a Windows operating system.

The non-linear mixed-effects modeling software NONMEM version 7.3.0 or older (ICON plc, Gaithersburg, MD) will be used for the population PK analysis. The stochastic approximation expectation-maximization (SAEM) with interaction computational algorithm will be used for model estimation. Standard errors at the final model parameter estimates will be calculated subsequently using the importance sampling approach (IMP) as implemented in NONMEM. Perl-speaks-NONMEM (PsN, version 4.6.0) will be used to operate NONMEM. Dataset preparation, exploratory analyses, processing of model outputs and model simulations will be performed using R software version 3.4.3 or older.

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

The definition for Full Analysis Set was rephrased to be clearer:

Definition in the Protocol:

All subjects enrolled in Part A will be included in the Full Analysis Set – Part A and all subjects enrolled 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 enrolled in the current study. This will be the analysis population for all analyses.

Definition in the SAP:

FAS Part A: The FAS Part A consists of all subjects who are screen success and who have at least one measure of buprenorphine or norbuprenorphine concentration in plasma or at least one measure of buprenorphine or norbuprenorphine concentration in urine (as free drug or from quantitative UDS) or at least one measure for buprenorphine qualitative UDS in Part A (from Scheduled or Unscheduled visits).

FAS Part B: The FAS Part B consists of all subjects who met continuation criteria for Part B and who have at least one measure of buprenorphine or norbuprenorphine concentration in plasma or at least one measure of buprenorphine or norbuprenorphine concentration in urine (as free drug or from quantitative UDS) or at least one measure for buprenorphine qualitative UDS in Part B (from Scheduled or Unscheduled visits).

The **FAS** consists of all subjects who are part of FAS Part A and/or FAS Part B.

18. REFERENCES

FDA Guidance for Industry - Population Pharmacokinetics. 1999

INDV-6000-M04. Population Pharmacokinetic and Exposure-Response Analyses for Buprenorphine after Repeated Subcutaneous Injections of RBP-6000 in Treatment-Seeking Subjects with Opioid Use Disorder. Indivior Modeling Report 2017

INDV-6000-M05. Population Pharmacokinetics of RBP-6000 in Treatment-Seeking Subjects with Opioid Use Disorder: Combined Analysis of Studies RB-US-12-0005, RB-US-13-0001 and RB-US-13-0003. Indivior Modeling Report 2017

19. APPENDIX

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 of the study protocol 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, 2 aliquots will be sent to the bioanalytical laboratory and 1 aliquot will be sent to the diagnostic laboratory, and 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 and serious 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.

APPENDIX 2: PARTIAL DATE IMPUTATION

Missing Severity in Adverse Events

If the severity is missing for an AE, then a severity of "Severe" will be assigned.

The imputed values for assessment will be used for incidence summary, while the actual values will be presented in data listings.

Missing Date Information for Adverse Events

When the AE start date is incomplete (i.e., partially missing), then the following rules will be applied:

Missing day and month

- If the year is the same as the year of the date of the first visit date in Part A, then the day and month of the date of the first visit date in Part A will be assigned to the missing fields.

- If the year is before the year of the first visit date in Part A, then December 31 will be assigned to the missing fields.

- If the year is after the year of the date of the first visit date in Part A, 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 first visit date in Part A, then the day of the first visit date in Part A will be assigned to the missing day.

- If either the year is before the year of the date of the first visit date in Part A or if both years are the same but the month is before the month of the first visit date in Part A, 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 visit date in Part A or if both years are the same but the month is after the month of the date of the first visit date in Part A, then the first day of the month will be assigned to the missing day.

If the start date is after the stop date after missing value calculation, the stop date will be used as the start date.

Missing Date Information for Concomitant Medications

For concomitant medications, incomplete (i.e., partial missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, consider imputing the start date first.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first visit date in Part A, then the day and month of the date of the first visit in Part A 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 visit date in Part A, 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 visit date in Part A, 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 first visit date in Part A, then the day of the first visit date in Part A will be assigned to the missing day.

- If either the year is before the year of the first visit date in Part A or if both years are the same but the month is before the month of the first visit date in Part A, 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 visit date in Part A or if both years are the same but the month is after the month of the first visit date in Part A, then the first day of the month will be assigned to the missing day.

Incomplete Stop Date

Missing day and month

- If the year of the incomplete stop date is the same as the year of the last visit date, then the day and month of the last visit date will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of the last visit date, then December 31 will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the last visit date, 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 last visit date, then the day of the last visit date will be assigned to the missing day.

- If either the year is before the year of the date of the last visit date or if both years are the same but the month is before the month of the last visit date, 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 visit date or if both years are the same but the month is after the month of the date of the last visit date, then the first day of the month will be assigned to the missing day.

In case that the start date is after the stop date after missing value calculation, the non-computed date will replace the computed date. If both are computed, replace the stop date with the start date.

APPENDIX 3: ANALYSIS WINDOW

For the analyses described in Section 13.1, visits are defined as follows:

- If a subject was not able to provide blood or urine collection at a scheduled visit and has the assessments performed at a later unscheduled visit, the unscheduled assessments will be mapped to the previous scheduled visit.

- If there are multiple unscheduled assessments, the one closest to the scheduled visit will be mapped.

APPENDIX 4: CORRECTION OF URINE CONCENTRATIONS OR URINE-TO-PLASMA CONCENTRATION RATIOS BY CREATININE CONCENTRATION IN URINE

Buprenorphine or norbuprenorphine urine concentration (C_{urine}) corrected by creatinine concentration in urine (C_{creat}) will be calculated as follows:

$$C_{urine,corr}(\mu g/g\ creatinine) = \frac{C_{urine}\ (ng/mL)}{C_{creat}(mg/dL)} \times 100$$

Buprenorphine or norbuprenorphine urine-to-plasma concentration ratio corrected by creatinine concentration in urine will be calculated as follows:

$$Ratio_{corr}(per\ mg/dL\ creatinine) = \frac{C_{urine}\ (ng/mL)}{C_{plasma}(ng/mL)} \times \frac{1}{C_{creat}(mg/dL)}$$

Of note:

$$C_{plasma}(ng/mL) = C_{plasma}(pg/mL)/1000$$

$$C_{urine}(ng/mL) = C_{urine}(pg/mL)/1000$$