Statistical Analysis Plan

NCT03993392

Study Number: INDV-6000-403

Title: An Open-label, Rapid Initiation Study for Extended-Release Buprenorphine Subcutaneous Injection (SUBLOCADE™)

SAP Date: 20 February 2020

Title Page

Protocol Title: An Open-label, Rapid Initiation Study for Extended-Release Buprenorphine Subcutaneous Injection (SUBLOCADE™)

Protocol Number: INDV-6000-403

Drug: SUBLOCADE™ (extended-release buprenorphine)

Short Title: SUBLOCADE Rapid Initiation Study

Sponsor Name: Indivior Inc.

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Regulatory Agency Identifier Number(s)

Registry	**ID**
ClinicalTrials.gov	CT04060654

Final v3.0: 20Feb2020

Statistical Analysis Plan Approval

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SAP Date: 20Feb2020, Version 3.0

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1 INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary, pharmacokinetic and statistical analyses of the data collected in Study INDV-6000-403.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified in Section 6.2. Any deviations from the analyses described below, as well as Post-hoc analyses, will be documented in the clinical study report (CSR).

Specification of tables, listings and figures (TLFs) are provided in a separate document.

1.1 Version History

Table 1 SAP Version History Summary

SAP Version	SAP Approval Date	Associated Protocol	Protocol Amendment Approval Date	Change	Rationale
1.0	09Sep2019	Amendment 1	14Aug2019	Not Applicable	Original version
2.0	19Dec2019	Amendment 1	14Aug2019	Described the COWS total score increase of ≥ 6 key endpoint in terms of the cumulative event rate.	To align with updated main analytical approach as Kaplan-Meier.
				Defined the evaluable subjects as having COWS assessments for the key timepoints.	To align with updated main analytical approach of survival analysis.
				Clarified definition of Full Analysis Set.	To align with updated main analytical approach of survival analysis.
				Clarified definition of PK Analysis Set.	To state number of concentration samples required for inclusion.
				Clarified definitions of baseline.	Clarification.

Table 1 SAP Version History Summary

SAP Version	SAP Approval Date	Associated Protocol	Protocol Amendment Approval Date	Change	Rationale
				Defined analysis phases.	To clarify analysis with respect to different study phases.
				Changed description of disposition summary.	To align with analysis phases.
				Added summary of entry criteria failed.	To facilitate reporting by supplementing the listing of failed entry criteria.
				Changed main analytical approach for COWS total score increase of ≥ 6 to Kaplan-Meier using key timepoints. Added stratification sensitivity analysis for number of TM BUP doses post-SUBLOCADE and enrolment before/after re-training.	To account for missing COWS assessments in the first 48 hours post-SUBLOCADE, which was unexpected. Evaluate impact of stratification variables on response.
				Added a sensitivity analysis of COWS total	In consideration of potential for informative missing COWS

Table 1 SAP Version History Summary

SAP Version	SAP Approval Date	Associated Protocol	Protocol Amendment Approval Date	Change	Rationale
				score increase of ≥ 6 utilizing event adjudication.	assessments in the first 48 hours post-SUBLOCADE.
				Corrected the equation for COWS AUC and clarified details of the calculation, including times used and normalization.	Correction and clarification.
				Clarified analysis of change from baseline COWS total scores and OC-VAS scores.	To align with clarification of baseline definitions.
				Clarified definition of precipitated withdrawal following induction dose of TM BUP.	To align with clarification of baseline definitions.
				Clarified calculation of AUC_{inf} for NMP	Clarification.

Table 1 SAP Version History Summary

SAP Version	SAP Approval Date	Associated Protocol	Protocol Amendment Approval Date	Change	Rationale
				Added conversion of unit for NMP plasma concentrations.	To present data using preferred unit.
				Added analysis phases to summary of exposure.	To present exposure according to study phases.
				Added analysis of AEs within 48 hours of SUBLOCADE dosing.	To evaluate AEs occurring during the interval defined by the key timepoints.
				Added AE summaries for the TM BUP Analysis Set.	To assess AEs prior to and following administration of SUBLOCADE.
				Added a listing of COWS total scores and AEs.	To evaluate AEs in relation to COWS total scores.
				Added summaries of Drug Use History for the FAS and enrolled populations.	To assess results in these populations.

Table 1 SAP Version History Summary

SAP Version	SAP Approval Date	Associated Protocol	Protocol Amendment Approval Date	Change	Rationale
				Added summary of subjects meeting liver function test review criteria.	To summarize this data rather than only list it.
				Clarify data source used for UDS and TLFB analysis.	Clarification.
				Modified analysis visit descriptors.	To align with visit description in the protocol.
				Corrected the categories of TM BUP dose to 1 dose and ≥ 2 doses.	Correction.
				Added demographics summaries for the subjects who did not enroll and enrolled populations.	To assess results in these populations.

Table 1 SAP Version History Summary

SAP Version	SAP Approval Date	Associated Protocol	Protocol Amendment Approval Date	Change	Rationale
				Removed definition of post-treatment medications.	Not needed for this study.
				Minor corrections of typographical errors and clarification throughout.	Corrections and clarifications.
3.0	20Feb2020	Amendment 1	14Aug2019	Update description of adjudication.	For alignment with draft charter.
				Clarify handling of BLQ concentrations.	Clarification.
				Add AESI as a category to overall summary table.	Correction, AESI was inadvertently omitted.
				Remove reference to post-study medications in Table 12.	Correction as post-study medication flags are not being utilized for analysis.
				In Table 12, clarify handling of non-study medications that are	Clarification.

Table 1 SAP Version History Summary

SAP Version	SAP Approval Date	Associated Protocol	Protocol Amendment Approval Date	Change	Rationale
				"ongoing" in assigning flags and missing times.	
				Renumber Section 5 subsections and correct typographical errors.	Correction.
				Described supplemental analysis: imputation of missing date/time for COWS assessments.	This imputation is needed in order to create the listing of COWS and AEs in chronological order as described Section 5.5.2.

1.2 Objectives and Endpoints

Table 2 Objectives and Endpoints

Objectives	Endpoints
	Key
• The objective of this study is to evaluate the safety and tolerability of initiating SUBLOCADE following a single dose of TM buprenorphine (TM BUP).	• Cumulative event rate of ≥ 6-point increase in Clinical Opiate Withdrawal Scale [COWS] total score from the pre-SUBLOCADE value within the first 1 hour (precipitated withdrawal), and 6, 12, 24, or 48 hours post SUBLOCADE administration. • Area under the curve (AUC) of COWS total score from the pre-SUBLOCADE value through 1, 6, 12, 24 and 48 hours after SUBLOCADE administration. • Total score on the COWS during the treatment period (i.e. at each assessment timepoint from administration of TM BUP at Day 1 through end-of-treatment (EOT)). • Score on the opioid craving visual analogue scale (OC-VAS) during the treatment period.
Tertiary/Exploratory	
	• Number and percentage of subjects who experience precipitated withdrawal from the first dose of TM BUP (defined as an increase in COWS by ≥6 from prior to the dose of TM BUP up to the pre-SUBLOCADE COWS assessment). • Peak and overall plasma exposure to N-methyl-2-pyrrolidone (NMP) following a single SC injection of 300 mg SUBLOCADE.
Other Safety Assessments	
	• Major safety endpoints will include the proportion of subjects with TEAEs of the following types at any time during the treatment period (i.e., any time

	after administration of TM BUP): TEAE, drug-related TEAE, serious TEAE, drug-related serious TEAE and TEAE leading to treatment discontinuation. • Additional safety endpoints will include assessment of laboratory results, vital signs and concomitant medications. • Withdrawal symptoms will be monitored by COWS (secondary endpoint), AEs, opioid craving (using OC-VAS; secondary endpoint) and sedation (using Sedation VAS).

1.3 Study Design

SUBLOCADE™ (extended-release buprenorphine) injection for subcutaneous (SC) use is currently indicated for the treatment of moderate to severe opioid use disorder (OUD) in patients who have initiated treatment with a transmucosal (TM) buprenorphine-containing product to suppress opioid withdrawal signs and symptoms for a minimum of 7 days (SUBLOCADE United States Prescribing Information [USPI]). This study is to evaluate the safety and tolerability of starting SUBLOCADE treatment following a shorter period of TM BUP treatment.

This is a Phase 4, non-randomized, uncontrolled, open-label, single group, single center study in approximately 15 adult subjects with moderate or severe OUD.

Subjects who provide written informed consent will enter a Screening Period to confirm study eligibility. On Day 1, eligible subjects will check-in to undergo pre-buprenorphine assessments and be evaluated to receive TM BUP. If a subject's COWS is not ≥8, the subject may either be re-scheduled for check-in within the Screening Period or remain in the clinic (at the Investigator's discretion), and the COWS may be repeated until the subject achieves a score ≥8. Only when the COWS is ≥8 and all pre-buprenorphine assessments have been completed may the subject receive TM BUP.

One hour after the TM BUP dose, the subject will complete pre-SUBLOCADE assessments including: COWS (first, to assess precipitated withdrawal) and OC-VAS, then Sedation VAS, AEs, vital signs and concomitant medications.

Any subject who displays any allergic/hypersensitivity reaction to buprenorphine will be discontinued from the study and will be followed up via telephone call 24 to 72 hours post dose.

Subjects experiencing precipitated withdrawal will be treated for withdrawal symptoms. If precipitated withdrawal occurs before SUBLOCADE administration, the TM induction may be restarted later on the same day at the discretion of the Investigator, based on the half-life of the opioid reported on the Timeline Follow Back. Alternatively, the Investigator may permit the subject to return to the facility on another day (within the Screening Period). Returning subjects will repeat all Day 1 scheduled assessments.

If the subject does not display any allergic/hypersensitivity reaction or clinical signs of sedation, and does not experience precipitated withdrawal, 300 mg SUBLOCADE may be administered to the subject.

Following SUBLOCADE administration, the subject will remain in the clinic for approximately 48 hours and will be assessed for safety and tolerability, as well as for any signs of precipitated withdrawal. Subjects will return to the clinic weekly, until the end-of-treatment (EOT) visit (28 days after SUBLOCADE administration).

Subjects who discontinue from the study after TM BUP administration, and before SUBLOCADE administration, will be contacted via telephone 24 to 72 hours after TM BUP administration to include assessment of AEs and concomitant medications only.

Sufficient subjects will be enrolled to ensure that 15 subjects receive SUBLOCADE and are evaluable for precipitated withdrawal; that is, 15 subjects having data for at least 1 COWS assessment before SUBLOCADE injection and COWS assessments for 48 hours after SUBLOCADE injection (see **Section 3**).

An overview of the schedule of assessments for the study overall is provided in Table 3 and the detailed schedule of assessments for the Injection Visit (Visit 2, Days 1-3) in Table 4. Of note, blood samples will be collected prior to and at various times following SUBLOCADE administration to characterise the peak and overall plasma exposure to N-methyl-2-pyrrolidone (NMP), the biocompatible solvent used in the SUBLOCADE formulation.

Table 3 Schedule of Assessments – Overview of Study

Procedure/Assessment	Screening	Injection[a]	1 week post dose	2 weeks post dose	3 weeks post dose	EOT[16]	EOS[17]	TM BUP ET[18]
Visit Number	1	2	3	4	5	6	7	
Day(s)	-30 to -1	1-3	8	15	22	29	43	24-72 hr Post-TM BUP dose
Window (days)			± 1	± 2	± 2	± 2	±5	
Informed Consent[1]	X							
Inclusion/Exclusion Criteria	X							
Demographics	X							
Medical/Psychiatric History	X							
Substance/Drug Use History[2]	X							
Physical Examination[3]	X					X		
Height/Weight/BMI[4]	X	X[a]				X		
Vital Signs[5]	X	X[a]	X	X	X	X		
12-Lead ECG[6]	X	X[a]				X		
AE Assessment	◄ X ►							
Concomitant Medications[7]	◄ X ►							
HIV-1/HIV-2, Hep B, Hep C Antibody[8]	X							
Haematology	X							
Serum Chemistry	X							
Liver Function Testing[9]		X[a]	X			X		
Urinalysis	X							
Urine Pregnancy Test[10]	X	X[a]				X		
Alcohol Breath Test		X[a]						

Table 3 Schedule of Assessments – Overview of Study

Procedure/Assessment	Screening	Injection[a]	1 week post dose	2 weeks post dose	3 weeks post dose	EOT[16]	EOS[17]	TM BUP ET[18]
Visit Number	1	2	3	4	5	6	7	
Day(s)	-30 to -1	1-3	8	15	22	29	43	24-72 hr Post-TM BUP dose
Window (days)			± 1	± 2	± 2	± 2	±5	
UDS[11]	X	X[a]	X	X	X	X		
Self-Reports/TLFB[12]		X[a]	X	X	X	X		
COWS	X	X[a]	X	X	X	X		
OC-VAS	X	X[a]	X	X	X	X		
Sedation VAS		X[a]						
Study Drug Administration		X[a]						
Injection Site Evaluation[13]		X[a]	X	X	X	X		
PK Sampling[14]		X[a]	X	X	X	X		
Counselling[15]		← X →						

AE=adverse event; ALP=alkaline phosphatase; ALT=alkaline aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; BUP=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; ECG=electrocardiogram; EOS=End-of-Study; EOT=End-of-Treatment; ET=Early Termination; GGT=gamma-glutamyl transferase; Hep=Hepatitis; HIV=human immunodeficiency virus; LD=lactase dehydrogenase; LFT=liver function tests; NMP=N-methyl-2-pyrrolidone; OC-VAS=Opioid Craving Visual Analogue Scale; OUD=opioid use disorder; PK=pharmacokinetics; TLFB=TimeLine Follow Back; TM=transmucosal; UDS=urine drug screen; VAS=Visual Analogue Scale

a See Table 4 for detailed schedule of events for Visit 2 (SUBLOCADE Injection)

1. Written informed consent must be obtained before any study-specific assessments/procedures are initiated.
2. Drug use history to include tobacco, alcohol and caffeine use; drugs of abuse (illicit and prescribed). Drugs of abuse and alcohol use will capture the drug class, compounds, and route, dose and frequency of use for lifetime and past 30 days use); and OUD history including MOUD history and prior overdose history.

3. Complete physical examination to include an assessment of general appearance, skin and extremities, head and neck, lymph nodes, eyes, ears, nose, throat, thyroid, neurological system, lungs, cardiovascular system, and abdomen (liver and spleen). The examination will not include a breast, pelvic or rectal exam, unless clinically indicated. Clinically significant abnormal changes from screening will be recorded as AEs.
4. Height will be measured only at the Screening Visit. Body mass index will be calculated within the database using weight and height.
5. Includes systolic and diastolic blood pressure, pulse rate, respiratory rate and oral temperature after the subject has been in a sitting position for ≥3 minutes.
6. An ECG will be collected after the subject has been in a supine position for ≥5 minutes.
7. Includes a review of any previous (taken within 30 days of providing written informed consent) and ongoing medications (including over-the-counter) and herbal supplements.
8. HIV-1/HIV-2, Hep B and Hep C antibody testing to be performed only in the absence of a positive (documented) medical history for these conditions.
9. A sub-set of serum chemistry to be performed including: ALP, ALT, AST, bilirubin, albumin, total protein, GGT and LD only. For increased LFTs, subject should be asked to return to the clinic for weekly repeat liver chemistry testing (ALP, ALT, AST, and total bilirubin) until resolved, stabilised or return to within baseline values, per Protocol Section 8.2.7.3.
10. Required for female subjects of childbearing potential only.
11. Qualitative test to be performed for all visits. Additional quantitative test to be performed on Day 1. Additional unscheduled UDS may be performed as necessary.
12. Details subjects illicit drug use, in addition to report question capturing frequency, route and date of last use.
13. Injection site will be evaluated for signs of attempted removal. Any injection site reactions or infections will be recorded as AEs.
14. A 2-mL blood sample will be collected for NMP PK analysis.
15. Subjects will receive counselling during the study as determined by local standard of care.
16. All subjects who receive SUBLOCADE (including those who wish to discontinue early), will be encouraged to attend the EOT visit 28 days after SUBLOCADE administration (Day 29). After enrolment, available treatment options for completed subjects will be discussed.
17. Any subject with ongoing AEs or concomitant medications at the EOT visit and is not continuing MOUD will also be followed up by phone 2 weeks later for the EOS visit (Day 43) to assess the ongoing AEs or concomitant medications only.
18. Subjects who discontinue from the study and have been administered TM BUP but have not been dosed with SUBLOCADE will be followed up via telephone within 24 to 72 hours to assess ongoing AEs and concomitant medications only.

Table 4 Schedule of Assessments – Visit 2: INJECTION

	Day 1															Day 2			Day 3
Procedure/Assessment	**Check -in[1]**	**Pre-TM BUP**	**TM BUP**	**Pre-SUB-LOCADE**	**SUB-LOCADE**	**Post-SUBLOCADE**													
Protocol Time (hours)			**-1**		**0**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**30**	**36**	**48**
Assessment Window (hours)						**±0.25**				**±1**							**±2**	
PK sampling window (min)				**-10**		**±2**			**±5**	**±15**								
UDS	X																	
Self-Reports/TLFB[2]	X																	
Urine Pregnancy Test[3]	X																	
Alcohol Breath Test[4]	X																	
COWS & OC-VAS[5]	X	X		X		X	X	X	X	X	X	X	X[6]	X[6]	X	X	X	X
Concomitant Medications[7]	←								X									→
AE Assessment	←								X									→
Sedation VAS		X		X		X			X		X	X	X[6]	X[6]	X	X	X	X
Vital Signs[8]		X		X		X			X		X	X			X	X	X	X
12-Lead ECG[9]		X													X			X
TM BUP administration			X[10]															
Liver Function Testing[11]			X[13]															
Weight[12]			X[13]															
SUBLOCADE administration					X[14]													
Injection Site evaluation[15]						X			X			X			X		X	X
PK Sampling[16]				X		X	X		X	X	X	X			X	X	X	X
Counselling[17]		←							X									→

Check Out of Clinic[18]																	X

AE=adverse event; ALP=alkaline phosphatase; ALT=alkaline aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; BUP=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; ECG=electrocardiogram; GGT=gamma-glutamyl transferase; PK=pharmacokinetics; OC-VAS=Opioid Craving Visual Analogue Scale; LD=lactase dehydrogenase; LFT=liver function test; TLFB=TimeLine Follow Back; TM=transmucosal; UDS=urine drug screen; VAS=Visual Analogue Scale

1. Upon arriving at the clinic, subjects will provide a urine sample for a UDS for qualitative and quantitative analysis, a urine sample for a pregnancy test (child-bearing females only), perform an alcohol breathalyser test and self-report their concomitant medications since screening and recent illicit drug use (including the use of a TimeLine Follow Back [TLFB]). If subject is deemed eligible for check-in the subject will then be assessed for withdrawal symptoms using COWS and for craving using OC-VAS.
2. Details subjects illicit drug use, in addition to report question capturing frequency, route and date of last use.
3. Required for female subjects of childbearing potential only.
4. Per Investigator's discretion, subjects with positive test may either remain in the clinic or be re-scheduled to return on another date.
5. Per Investigator's discretion, subjects with COWS <8 may either remain in the clinic and repeat assessments at a later time or be re-scheduled to return on another date. The COWS may be repeated at any time, per Investigator's discretion, and should always be repeated just before TM BUP and SUBLOCADE administration. The OC-VAS should be performed each time a COWS assessment is performed.
6. If the subject is asleep at 16 and 20 hours, the assessments will not be performed, and the reason should be noted in the CRF.
7. Includes a review of any previous (taken since screening) and ongoing medications (including over-the-counter) and herbal supplements.
8. Includes systolic and diastolic blood pressure, pulse rate, respiratory rate and oral temperature after the subject has been in a sitting position for ≥3 minutes.
9. An ECG will be collected after the subject has been in a supine position for ≥5 minutes.
10. Eligible subjects must meet the buprenorphine dosing criterion, prior to receiving 4mg TM BUP.
11. A sub-set of serum chemistry to be performed including: ALP, ALT, AST, bilirubin, albumin, total protein, GGT and LD only. For increased LFTs, subject should be asked to return to the clinic for weekly repeat liver chemistry testing (ALP, ALT, AST, and total bilirubin) until resolved, stabilised or return to within baseline values, per protocol Section 8.2.7.3.
12. Weight to be captured; BMI will be calculated in the database using height from screening.
13. Assessment to be performed anytime pre-SUBLOCADE dose.
14. Eligible subjects meet SUBLOCADE dosing criteria, prior to receiving SUBLOCADE.
15. Injection site will be evaluated for signs of attempted removal. Any injection site reactions or infections will be recorded as AEs.
16. A 2-mL blood sample will be collected for NMP PK analysis at each time point. The PK samples should be collected as closely as possible to the nominal times, permitted windows are present in the header in minutes. The pre-dose PK sample should be performed after the subject has been confirmed eligible for SUBLOCADE dosing.
17. Subjects will receive counselling during the visit as determined by local standard of care.
18. Subjects will check out of clinic upon completion of all scheduled assessments.

2 STATISTICAL HYPOTHESES

For this single arm study, the analysis methods are estimation (for cumulative event rate of COWS increase ≥ 6 within the first 1, 6, 12, 24, and 48 hours) and description (COWS AUC within the first 1, 6, 12, 24, and 48 hours, and COWS and OC-VAS absolute scores and change from pre-treatment values at each timepoint). Therefore, statistical testing and hypotheses are not applicable.

2.1 Multiplicity Adjustment

There is no multiplicity adjustment.

3 SAMPLE SIZE DETERMINATION

Approximately 15 adult subjects with moderate to severe OUD are planned to be dosed with SUBLOCADE. Additional subjects may be enrolled to ensure that 15 subjects are dosed with SUBLOCADE and are evaluable for the key timepoints defined as 1, 6, 12, 24, and 48 hours post-SUBLOCADE (see Section 5.3.1.)

With a sample size of 15, the probability to observe at least one case of precipitated withdrawal is 79.4%, assuming the true event rate is 10%, while the probability to observe at least one case of precipitated withdrawal is reduced to 53.7% if the true event rate is 5%. Table 5 provides the probabilities of observed events at different true event rates.

Table 5 Probabilities of Observed Events at Different True Event Rates

True Event Rate	0 event	At Least 1 Event	At Least 2 Events	At Least 3 Events
1%	0.860	0.140	0.010	0.0004
5%	0.463	0.537	0.171	0.036
8%	0.286	0.714	0.340	0.113
10%	0.206	0.794	0.451	0.184
15%	0.087	0.913	0.681	0.396
20%	0.035	0.965	0.832	0.602

4 POPULATIONS FOR ANALYSIS

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

Table 6 Populations for Analysis

Population	Description
Screened	All subjects who sign the informed consent document.
Enrolled	A subject will be considered enrolled if he/she receives at least 1 dose of TM BUP.

Full Analysis Set	The FAS population consists of all subjects who receive a SUBLOCADE injection and have data for at least 1 COWS assessment at the Pre-SUBLOCADE timepoint just before the SUBLOCADE injection and a COWS assessment for at least one of the scheduled timepoints within 48 hours after SUBLOCADE injection. The FAS will serve as the primary population for the analysis of key endpoints in this study.
Safety Analysis Set	The safety population will be used for the safety analysis, and it consists of all subjects who received at least 1 dose of SUBLOCADE. The safety population will serve as the primary population for the analysis of safety assessments related to SUBLOCADE.
TM BUP Analysis Set	The TM BUP Analysis Set consists of all subjects who received at least 1 dose of TM BUP. This analysis set will be used for analysis of the exploratory safety endpoint related to TM BUP. (Note: this is the same population as Enrolled).
PK Analysis Set	The PK Analysis Set will be used for the Exploratory PK endpoint analysis and will consist of all subjects who received the SUBLOCADE injection and have at least one NMP plasma concentration measurement post-SUBLOCADE. Subjects in the PK population with protocol deviations or events that impact the quality of the PK data will be assessed on a case-by-case basis.

5 STATISTICAL ANALYSES

5.1 General Considerations

5.1.1 Statistical Analyses and Coding

Statistical analyses will be performed using version 9.4 (or higher) of SAS.

The non-compartmental PK analysis of NMP data will be performed using Phoenix WinNonlin version 8.1 or higher (Certara, Princeton, NJ).

The AEs and medical/psychiatric history will be coded using the latest version of MedDRA available at the time of database lock.

The concomitant medications will be coded using the latest version of the World Health Organization (WHO) Drug Dictionary.

The final analysis will occur after the database lock.

5.1.2 Treatment Labels

The treatment labels will be presented in the tables, listings and figures (TLFs) as either

SUBLOCADE 300mg, or

TM Buprenorphine only or TM BUP only

as applicable to the analysis population being presented.

5.1.3 Definition of Pre-TM BUP Value, Pre-SUBLOCADE Value, and Pre-SUBLOCADE Baseline

For analyses of COWS and OC-VAS (i.e., the key and exploratory endpoints), the Pre-TM BUP value is the measure obtained at the Pre-TM BUP timepoint just before a TM-BUP dose for induction, and the Pre-SUBLOCADE value is the measure obtained at the Pre-SUBLOCADE timepoint just before the SUBLOCADE injection.

For the analysis of other safety assessments (described in Section 5.5), the Pre-SUBLOCADE baseline will be the last non-missing value prior to the administration of SUBLOCADE.

5.1.4 Definition of Analysis Phases

Screening phase: starts from the date of screening visit and ends at the date/time of the first TM-BUP dose for induction.

Induction phase: starts from the date/time of the first TM-BUP dose for induction and ends at the date/time of SUBLOCADE injection or TM-BUP ET visit.

SUBLOCADE treatment phase: starts from the date/time of SUBLOCADE injection through the date of last visit in the study (EOT or EOS, whichever is applicable).

The overall treatment period for the study is the combination of induction and SUBLOCADE treatment phases.

5.1.5 General Conventions for Analysis

If the FAS and safety analysis sets comprise the same set of subjects, analyses indicated to be performed on both populations will be performed only on the FAS population.

Continuous variables will be summarised using the descriptive statistics mean, standard deviations (SD), median, minimum and maximum, unless other statistics are specified. 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 EOS (including unscheduled visits), i.e., for the Screened Population unless otherwise specified.

Figures presenting summary data will include scheduled visits and assessments only. Figures of individual subject data will include all visits, scheduled and unscheduled. Visits will be presented chronologically.

Observed data is used for analysis, unless handling of missing data is described otherwise within the analysis description or in Section 6.5.

5.2 Subject Dispositions

The number and percentage of subjects who were screened and enrolled or not enrolled, and the reasons for not enrolling, will be summarized for the Screened population. For the Enrolled population, the number and percentage of subjects who received SUBLOCADE, completed the study, discontinued and the reasons for discontinuing during the induction or the SUBLOCADE phase, will be summarized.

The number and percentage of subjects comprising each analysis population will be summarized.

The number and percentage of subjects failing entry criteria will be summarized overall and by individual criterion for the Screened population.

5.3 Key Endpoints Analysis

The analysis of key endpoints will be performed using the FAS, unless otherwise specified. The derived endpoints will be listed for the FAS.

The key timepoints for the analysis are defined as 1, 6, 12, 24, and 48 hours post-SUBLOCADE.

5.3.1 COWS Total Score Increase by ≥6 - Definition of Endpoint(s)

The total score on the COWS assessment at each timepoint will be calculated as the sum of the 11 individual item scores at the timepoint. Incomplete COWS assessments are not expected. (Note the term COWS will refer to COWS total score throughout this section.)

The endpoint is the cumulative event rate of an increase in COWS total score by ≥6 from the pre-SUBLOCADE value.

5.3.2 COWS Total Score Increase by ≥6 - Main Analytical Approach

The cumulative event rate for COWS Total Score increase by ≥6 from the pre-SUBLOCADE value will be estimated via the Kaplan-Meier method (1958), using the 5 key timepoints, 1, 6, 12, 24 and 48 hours after SUBLOCADE administration (i.e., time=0). Note that for the 1-hour key timepoint the event is referred to as precipitated withdrawal. A subject will be considered in the risk evaluation set at a specific key timepoint if the subject had a pre-SUBLOCADE COWS assessment and either 1) an increase in COWS by ≥6 from the pre-SUBLOCADE value within the current time interval (from the previous key timepoint to the current key timepoint), or 2) had a COWS assessment at the current key timepoint and all the prior key timepoints. If a subject has missing COWS assessment at one or more above key timepoints (1, 6, 12, 24 and 48 hours after SUBLOCADE administration), the subject is censored at the last key timepoint prior to the first missing timepoint.

The values for the event occurrence, time, and censoring parameters are assigned sequentially for the subject disposition events according to the order and criteria in Table 7.

Table 7 Parameters for Kaplan-Meier Method

Order of assignment	Disposition Event	Event of COWS Total Score Increase by ≥6	Time (hours)	Censored
1	An increase in COWS total score by ≥6 from the pre-SUBLOCADE value at any timepoint (scheduled or unscheduled) within 48 hours after SUBLOCADE injection	Yes	Nominal time of the first key timepoint on or after the COWS assessment meeting an increase in COWS total score by ≥6 from the pre-SUBLOCADE value	No
2	Missing COWS assessment at a key timepoint and without an increase in COWS total score by ≥6 from the pre-SUBLOCADE value within 48 hours	No	Nominal time of last key timepoint prior to the first missing key timepoint (i.e., 0, 1, 6, 12 or 24)	Yes
3	Completed COWS assessment at 1, 6, 12, 24, and 48 hours and without an increase in COWS total score by ≥6 from the pre-SUBLOCADE value within 48 hours	No	48	Yes

A Kaplan-Meier plot of the cumulative event rate from time=0 to 48 hours will be produced.

5.3.3 COWS Total Score Increase – Sensitivity Analyses

5.3.3.1 Stratification Variables

If sample size permits, the cumulative event rate analysis will be repeated for each of three stratification variables: number of TM BUP doses during induction phase (1 dose, ≥ 2 doses) and during SUBLOCADE treatment phase (0 dose, >=1 dose), and by enrollment before or after re-training (see Section 5.6).

5.3.3.2 Event Adjudication

An event adjudication committee, consisting of members external to Indivior, will perform adjudication of the data. The committee will review data from enrolled subjects and based on their clinical judgement, assess for each subject:

- whether precipitated withdrawal occurred following TM BUP
- whether precipitated withdrawal occurred within 48 hours post-SUBLOCADE injection, and if so at what study timepoint it occurred

The details of the adjudication committee membership and process will be defined in a committee charter.

The frequency count, percentage and its 2-sided 95% exact confidence interval (CI) using binomial distribution Clopper-Pearson method (Clopper 1934) will be constructed for adjudicated precipitated withdrawal following TM BUP and adjudicated precipitated withdrawal within 48 hours post-SUBLOCADE injection. The analysis for adjudicated precipitated withdrawal post-SUBLOCADE injection will be performed cumulatively by timepoint if there are any adjudicated events.

5.3.4 Normalized AUC for COWS Total Score Post-SUBLOCADE Injection - Definition of endpoint

The area under the curve (AUC) for COWS total score from the pre-SUBLOCADE value to a later time point will be calculated using the linear trapezoidal method, i.e.,

$$AUC = \frac{1}{2}\sum_{i=0}^{n} (T_{i+1} - T_i)(C_{i+1} + C_i)$$

where T_0 is the time of the SUBLOCADE injection, C_0 is the COWS total score at the pre-SUBLOCADE timepoint, T_i is the i^{th} time value, C_i is the i^{th} COWS total score, and n is the number of time values. Inherent to this formula, intermittent missing COWS total scores are imputed in a linear manner.

For each analysis time interval ($AUC_{0\text{-}1hr}$, $AUC_{0\text{-}6hrs}$, $AUC_{0\text{-}12hrs}$, $AUC_{0\text{-}24hrs}$, $AUC_{0\text{-}48hrs}$) the AUC value will be normalized across subjects for the actual duration (in hours) of the time interval. The formula for normalized AUC for a given subject in a given analysis time interval is:

$AUC_{normalized}$=$AUC_{calculated}$ divided by the actual duration of time interval (hrs)

Note: the normalized AUC for COWS can be interpreted as the averaged AUC per hour or the averaged COWS over a time interval, as if the COWS was measured hourly during that time interval. For example, the $AUC_{0\text{-}1hr}$ is the average of the COWS total scores assessed at time= 0 and time=1 hour. $AUC_{0\text{-}6hrs}$ is the average of the COWS total scores assessed from time= 0 to time=6 hours, as if the COWS total score was assessed hourly.

5.3.5 Normalized AUC for COWS Total Score Post-SUBLOCADE Injection - Main analytical approach

The normalized AUC of COWS from the pre-SUBLOCADE value (i.e., time=0) through the key scheduled time points of 1, 6, 12, 24 and 48 hours (i.e., the analysis time intervals) after SUBLOCADE administration will be summarized using descriptive statistics for continuous endpoints.

A subject is included in a given analysis time interval if the subject has both the pre-SUBLOCADE COWS value (i.e., non-missing COWS at time=0) and the COWS assessment at the terminal scheduled timepoint for that analysis time interval or at a later timepoint up to 48 hours. Intermittent missing COWS total scores at a key timepoint other than 48 hours will be imputed via linear interpolation using the closest non-missing COWS total scores before and after the missing COWS total score. The two closest non-missing COWS total scores and their associated timepoints are defined as (C_b, T_b) and (C_a, T_a) where b=before and a=after. The imputed value for the missing COWS total score, for C_m, is

$$C_m = C_b + (T_m - T_b)\frac{C_a - C_b}{T_a - T_b}$$

where T_m is the imputed time as defined below.

Thus, the missing COWS total score at the terminal scheduled timepoint for the analysis interval will not be imputed if there is no observed COWS total score following that timepoint up to 48 hours, and subjects with such missing COWS total score will be excluded from the calculation for that analysis interval. All observed COWS total scores (at scheduled timepoints and unscheduled timepoints with a non-missing time) within the analysis interval of interest will be used. The actual time will be used for calculation. If the actual time for a scheduled assessment is missing, the time will be imputed for the AUC calculation as

$\text{Time}_{\text{current COWS}}$=actual time $_{\text{SUBLOCADE injection}}$ + nominal $\text{time}_{\text{current COWS}}$

5.3.6 Normalized AUC for COWS Total Score Post-SUBLOCADE Injection – Sensitivity Analysis

The normalized AUC analysis described in Section 5.3.5 will be repeated, stratified by number of TM BUP doses during induction phase (1 dose, ≥ 2 doses) and during SUBLOCADE treatment phase (0 dose, >=1 dose), and by enrollment before or after re-training (Section 5.6).

5.3.7 COWS Total Score Absolute Value and Change - Definition of Endpoint

The endpoints are the COWS total score at each scheduled assessment timepoint from the Pre-TM BUP timepoint for the last TM BUP dose during the induction phase through EOT (i.e., absolute value), and the change in COWS total score from the pre-TM BUP and pre-SUBLOCADE values at each timepoint.

5.3.8 COWS Total Score Absolute Value and Change - Main Analytical Approach

The absolute value and change in COWS total score will be summarized using descriptive statistics at each scheduled nominal timepoint. The summary for COWS values will start from the Day 1 Check-in timepoint for the last TM BUP dose in the induction phase through EOT. The summary for change in COWS total score from the Pre-TM BUP value or from the Pre-SUBLOCADE value will start from the first scheduled nominal timepoint post the last TM BUP dose in the induction phase or the SUBLOCADE injection through EOT.

The analysis will use observed data and will include subjects with the pre-TM BUP/pre-SUBLOCADE value and a COWS assessment at the scheduled timepoint of interest.

The mean COWS total scores (absolute value and change from pre-TM BUP and pre-SUBLOCADE) will be plotted over time for all scheduled timepoints.

5.3.9 COWS Total Score Absolute Value and Change – Supplemental Analysis

Individual subject plots of COWS absolute value over time will be produced, using the TM BUP analysis set and including all assessment timepoints (scheduled and unscheduled).

If the actual date/time for a scheduled COWS assessment is missing, the date/time will be imputed for the purpose of creating the AE and COWS listing (Section 5.5.2):

$\text{Date/Time}_{\text{current COWS}} = \text{actual date/time}_{\text{SUBLOCADE injection}} + \text{nominal time}_{\text{current COWS}}$

5.3.10 OC-VAS Score Absolute Value and Change - Definition of endpoint

The OC-VAS score at each timepoint is the value marked on the paper source by the subject and recorded in the eCRF by site personnel.

The endpoints are the OC-VAS score at each scheduled assessment timepoint from Pre-TM BUP timepoint for the last TM BUP dose during the induction phase through EOT (i.e., absolute value), and the change in OC-VAS score from the pre-TM BUP and pre-SUBLOCADE values at each timepoint.

5.3.11 OC-VAS Score Absolute Value and Change - Main Analytical Approach

The absolute value and change in the OC-VAS score will be summarized using descriptive statistics. The summary for OC-VAS scores will start from the Day 1 Check-in timepoint for the last TM BUP dose in the induction phase through EOT. The summary for change in OC-VAS score from the Pre-TM BUP value or from the Pre-SUBLOCADE value will start from the first scheduled nominal timepoint post the last TM BUP dose in the induction phase or the SUBLOCADE injection through EOT.

The analysis will use observed data and will include subjects with at least one pre-TM BUP/pre-SUBLOCADE OC-VAS assessment and an OC-VAS assessment at the timepoint of interest.

The mean OC-VAS scores (absolute value and change from pre-TM BUP and pre-SUBLOCADE) will be plotted over time for all scheduled timepoints.

5.3.12 OC-VAS Score Absolute Value and Change – Supplemental Analysis

Individual subject plots of OC-VAS score absolute value over time will be produced, using the TM BUP analysis set and including all assessment timepoints (scheduled and unscheduled).

5.4 Exploratory Endpoint(s) Analysis

5.4.1 Precipitated Withdrawal from TM BUP – Definition of Endpoint

Precipitated withdrawal from a TM BUP induction dose will be defined as an increase in COWS by ≥6 from the Pre-TM BUP value for that TM BUP dose to the subsequent COWS assessment prior to the SUBLOCADE injection or the next TM BUP dose in the induction phase.

5.4.2 Precipitated Withdrawal from TM BUP – Main Analytical Approach

The frequency count, percentage and its 2-sided 95% exact confidence interval (CI) using binomial distribution Clopper-Pearson method (Clopper 1934) will be constructed for precipitated withdrawal from the first dose of TM BUP. The analysis will use observed data. A subject is considered eligible for the analysis if the subject has the Pre-TM BUP COWS assessment and a subsequent COWS assessment prior to the SUBLOCADE injection or the next TM BUP dose in the induction phase.

5.4.3 Peak and Overall Plasma Exposure to NMP – Definition of Endpoint

In addition to NMP plasma concentrations, the following PK parameters for NMP will be derived by non-compartmental analysis:

- C_{max}: maximum observed plasma concentration
- T_{max}: time of maximum observed plasma concentration
- $AUC_{0\text{-}24hr}$: area under the plasma concentration-time curve from time 0 to 24 hours post-SUBLOCADE dose.
- AUC_{last}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule.
- AUC_{inf}: area under the plasma concentration-time curve from time 0 extrapolated to infinite time.

$$AUC_{\text{inf}} = AUC_{last} + \frac{C_{last}}{\lambda_z}$$

AUC_{inf} will be reported if the percent of extrapolation is less than 20% and if the coefficient of determination Rsq is at least 0.8. A minimum of three data points will be required. C_{last} is the last quantifiable plasma concentration, λz is the slope of the terminal phase in semi-logarithmic scale.

5.4.4 Peak and Overall Plasma Exposure to NMP – Main Analytical Approach

NMP plasma concentrations will be reported by the bioanalytical laboratory in units of ng/mL and converted to µg/mL (result $_{\mu g/mL}$ = result $_{ng/mL}$ / 1000) for analyses and listings.

NMP plasma concentrations will be summarized descriptively (number of observations, mean, SD, median, minimum, maximum, geometric mean and coefficient of variation) at each scheduled sampling time for the PK Analysis set.

Plasma concentration values reported as below the limit of quantitation (BLQ) will be treated as zero to calculate summary statistics of plasma concentration data.

Linear and semi-logarithmic plots of the mean NMP plasma concentration-time curves will be presented. Plots of individual plasma concentration-time curves will also be presented on linear and semilogarithmic scales with all subjects shown on a same figure. Individual time plots will present all concentrations measured for the subject using actual sampling times. Mean plots will present concentrations measured at the scheduled sampling times.

Individual plasma concentration data will be presented in the listings for all subjects.

For the calculation of PK parameters, actual sampling times, rather than scheduled sampling times, will be used. In addition, all plasma concentrations that are BLQ prior to the first measurable concentration will be set to zero. The BLQ values that are between measurable concentrations 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. The BLQ values following the last quantifiable time points will be set to missing. No concentration estimates will be imputed for missing sample values.

Summary statistics (number of observations, mean, SD, median, minimum, maximum, geometric mean and coefficient of variation) will be calculated for all relevant PK parameters. Individual PK parameters will be presented in the listings.

5.5 Analysis of Other Safety Assessments

The analysis of the Other Safety Assessments will utilize the safety analysis set, unless otherwise specified.

See Section 6.5 for methods to handle missing safety data (e.g., partial dates).

5.5.1 Extent of Exposure

The extent of exposure will be summarized using the Enrolled Population. The number and percentage of subjects who received 1, 2, 3, etc. doses of TM BUP 4mg (i.e., the cumulative dose) during the induction and the SUBLOCADE treatment phases, and the number of subjects who received SUBLOCADE 300mg, will be summarized.

5.5.2 Adverse Events

A treatment emergent adverse event (TEAE) is defined as an AE observed after administration of the first TM BUP dose. The investigator determines the intensity of AEs and the relationship of AEs to study medication.

If a subject experiences an event both prior to the first dose of TM BUP and ongoing during the treatment, the event will be considered a TEAE (of the treatment) only if it has worsened in severity (i.e., it is reported with the date of worsening as the new start date/time) after starting administration of the TM BUP.

A TEAE summary table will present the number and percentage of subjects reporting a TEAE in the categories listed in Table 8.

Table 8 TEAE Summary Categories

Category
Subjects with Any TEAEs
With Study Medication-Related TEAEs
With Serious TEAEs (SAE)
With Study Medication-Related Serious TEAEs
With Severe TEAEs
With TEAE Leading to Death
With TEAE Leading to Study Medication Discontinuation
With TEAE Leading to Study Medication Interruption
With Serious TEAE Leading to Study Medication Discontinuation
With Serious TEAE Leading to Study Medication Interruption
With Adverse Events of Special Interest

The number and percentage of subjects reporting TEAEs during the treatment period will be presented by MedDRA system organ class (SOC) and preferred term (PT), each in descending order of frequency (then alphabetically in case of ties). The categories of TEAE listed above in Table 8 will be summarized in the same manner. TEAEs will also be summarized by intensity, system organ class and preferred term. The number of occurrences of TEAEs and study medication-related TEAEs will be summarized by PT. In addition, the number and percentage of fatal and fatal study medication-related treatment-emergent SAEs will be summarized separately by PT.

The summaries also will be presented for those AEs having a start date within 48 hours of the SUBLOCADE administration. These events will be defined as TEAEs where $0 \leq$ (AE start date -SUBLOCADE injection date) ≤ 2 days, and $0 \leq$ (AE start date/time -SUBLOCADE injection date/time) ≤ 48 hours.

In addition, the summaries of TEAEs, serious TEAEs, and related TEAEs will be presented for the TM BUP Analysis Set, separately for events with a start date/time during the Induction Phase and with a start date/time after the SUBLOCADE injection.

If more than one TEAE is coded to the same PT for the same subject, the subject will be counted only once for that PT using the most severe and most related occurrence for the summarizations by severity and by relationship to the study medication.

Listings will be presented for subjects with AEs, SAEs, AEs leading to discontinuation, and subjects who died (if any).

A chronological listing of COWS assessment dates/times and values, with AEs starting in each assessment interval, and administration dates/times of study medications will be produced.

5.5.3 Adverse events of special interest (AESI)

Adverse events of special interest are:

- SUBLOCADE depot removal
- Occurrences of ALT ≥3 × ULN and bilirubin ≥2 × ULN (> 35% direct)

The AESI will be included in the AE and SAE summaries as reported and flagged as AESI in the data listings.

5.5.4 Vital Signs

The results of scheduled assessments of vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and oral temperature), including absolute values and change from the pre-SUBLOCADE baseline will be summarised at each time point.

5.5.5 Electrocardiogram Data

At each scheduled timepoint, absolute values and change from the pre-SUBLOCADE baseline of ECG numeric variables (pulse rate, PR interval, QRS duration, QT Interval, and QT interval corrected using Fridericia's method) will be summarised.

The investigator's assessment of ECG results (normal/abnormal and if abnormal, clinically significant yes/no) will be listed.

5.5.6 Clinical Laboratory Tests

All laboratory data (including unscheduled and re-check values if present) will be listed chronologically.

For analysis of liver function tests, see Section 5.5.8.5.

5.5.7 Sedation VAS

At each time point, absolute value and change from the pre-SUBLOCADE Baseline of Sedation VAS will be summarised using observed data.

5.5.8 Other Safety Variables

The results of scheduled assessments of pregnancy tests, medical/psychiatric history, substance/drug use history, concomitant medications and liver function will be summarised and listed. The analyses will be performed using the safety analysis set, unless otherwise specified. See Section 6.5 for methods to handle missing data. Further analysis details are provided below.

5.5.8.1 Pregnancy Tests

The pregnancy test result data will be listed.

5.5.8.2 Medical/psychiatric history

The number and percentage of subjects reporting medical history events will be tabulated by SOC and PT, by decreasing frequency, using observed data.

5.5.8.3 Drug Use History

In addition to the safety analysis set, the analysis of drug use history will be performed on the FAS and enrolled populations.

Dates of drug use history are collected as month and year.

The overall lifetime drug use across all substances in years will be derived by subject as (the latest Stop Date – the earliest Start Date +1)/12.

In addition, the lifetime use in years will be derived for each drug class by subject, as the sum of the [(Stop Date – Start Date +1) / 12] for each drug in the class used by the subject. Where use of individual drugs within a class overlaps, this overlapped time will not be double-counted in the derivation.

For these derivations, missing end dates (month and year are missing) are set to the month and year of first study medication dose of TM BUP for induction. Partial dates (i.e., only year is collected) will be imputed as follows:

- Partial start dates are set to the first month of the year.
- Partial end dates are set to the last month of the year.

The number and percentage of subjects reporting each drug class, the years of lifetime use overall and for each drug class, and the use in the last 30 days will be summarized using observed data.

An additional analysis will summarize the number and percentage of subjects at each visit who use any opioid via the I.V route.

A listing of history of opioid use and other drugs of abuse will be provided (drug class, drug, route, dose and units, frequency, start/end dates, lifetime use in years, and last 30 days use). A missing end date will be presented as "ongoing" in the listing.

5.5.8.4 Prior and Concomitant Medications

Prior and concomitant medications will be summarised relative to the date of first TM BUP dose in the induction phase. The number and percentage of subjects with a prior/concomitant medication will be presented by pharmacological group (ATC level 3) and preferred drug name, sorted by decreasing frequency (then alphabetically in case of ties). In addition, the prior/concomitant medications will be listed.

For the definitions of prior and concomitant medications, see Section 6.8. Note that a given medication may be considered both prior and concomitant under these definitions, depending on missing start and end dates. Therefore, the prior/concomitant medication summary tables are not mutually exclusive.

5.5.8.5 Liver Function Tests

The absolute values and change from the pre-SUBLOCADE baseline of scheduled liver function tests (LFTs) will be summarised for the pre-SUBLOCADE baseline and the SUBLOCADE treatment period.

The frequency count and percentage of subjects meeting the protocol-specified liver chemistry review criteria (as below) will be summarized at pre-SUBLOCADE baseline and during the SUBLOCADE treatment period using assessments at both scheduled and unscheduled visits:

- ALT >3 × ULN and bilirubin >2 × ULN
- ALT >3 × ULN (and bilirubin ≤ 2 × ULN)
- ALT >5 × ULN but <8 × ULN
- ALT ≥8 × ULN

All LFT data (including unscheduled and re-check values if present) will be listed chronologically.

5.5.8.6 Urine Drug Screen (UDS) qualitative and TimeLine Follow Back (TLFB)

For each visit after Screening, data from the qualitative UDS results entered in the eCRF and TLFB will be combined to derive the number and percentage of subjects with positive opioid use, using observed data. The derivation will be applied according to Table 9.

Table 9 Opioid Use Derivation Based on eCRF Qualitative UDS and TLFB Results at a Given Visit

		TLFB Opioids		
		Missing	**Did not use**	**Use**
UDS Opioids	**Missing**	missing	negative	positive
	Negative	negative	negative	positive
	Positive	positive	positive	positive

For this analysis, opioids will include the eCRF results for opioids, buprenorphine (TLFB only), methadone, fentanyl, oxycodone, and morphine. If the result for any of these are positive, the subject will be considered positive for opioids.

The usage of individual substances collected via the UDS and TLFB will be listed.

5.5.8.7 Urine Drug Screen (UDS) Central Laboratory (Day 1)

The results collected via the central laboratory UDS on Day 1 will be listed.

5.6 Subgroup analyses

No subgroup analyses are planned for this study. However, where specified above for key endpoints and where sample size permits, the following stratification variables will be utilized:

- Number of TM BUP doses during the induction phase (1 dose, ≥ 2 doses)
- Number of TM BUP doses during SUBLOCADE treatment phase (0 dose, >=1 dose)
- Enrollment (i.e., first induction dose of TM BUP) before or after re-training on 08Oct2019

5.7 Interim Analyses

No formal interim analyses are planned for this study.

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1 List of Abbreviations

Table 10 List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alkaline aminotransferase
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
$AUC_{0\text{-}24hr}$	area under the plasma concentration-time curve from time 0 to 24 hours post-SUBLOCADE dose
AUC_{last}	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_{inf}	area under the plasma concentration-time curve from time 0 extrapolated to infinite time
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed concentration
COWS	Clinical Opiate Withdrawal Scale
CRF/eCRF	case report form/electronic case report form
CSR	clinical study report
ECG	electrocardiogram
EOS	end of study
EOT	end-of-treatment
ET	early termination

Abbreviation	Term
FAS	full analysis set
GGT	gamma-glutamyl transferase
Hep	hepatitis
HIV	human immunodeficiency virus
hr(s)	hour(s)
KM	Kaplan-Meier
LD	lactase dehydrogenase
LFT	liver function tests
MedDRA	Medical Dictionary for Regulatory Activities
MMP	medical monitoring plan
N/A	not applicable
NMP	N-methyl-2-pyrrolidone
OC-VAS	Opioid Craving Visual Analogue Scale
OUD	opioid use disorder
PK	pharmacokinetic(s)
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	System Organ Class
T_{max}	time of maximum observed plasma concentration
TEAE	treatment-emergent adverse event
TLF	tables, listings and figures
TLFB	timeline follow back
TM BUP	transmucosal buprenorphine
UDS	urine drug screen
ULN	upper limit of normal
USPI	United States Prescribing Information
VAS	visual analogue Scale
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

6.2 Appendix 2: Changes to Protocol-Planned Analyses

The main analytical approach for the analysis of increase in COWS total score of ≥6 from the pre-SUBLOCADE value is the Kaplan-Meier method. This method was described as a potential sensitivity analysis in version 1.0 of the SAP but is now specified as the main analysis given the extent of missing COWS assessments in the data. The endpoint is described accordingly as the cumulative event rate.

The protocol indicated that clinical laboratory tests assessed both at pre-SUBLOCADE and EOT would be summarized (Protocol Section 14.5.4). However, per the protocol schedule of assessments, clinical laboratory tests other than LFTs are only assessed at the screening visit. Therefore, tests other than LFTs are only listed.

The AUC formula has been corrected and details of the AUC analysis are provided to clarify imputation of missing COWS assessments, times used for the calculation, and to add normalization of the AUC.

The shift analysis of the investigator's assessment of ECGs is removed and the data will only be listed.

The protocol definition of precipitated withdrawal following TM BUP is corrected.

The pregnancy test result data will be listed only, and not summarized as stated in the protocol.

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

Nominal visits will be used for the analysis without regard to visit windows.

The mapping of the protocol/CRF visits to the analysis visits will be implemented as follows in Table 11. Unscheduled visits will be given an analysis visit number in sequential order according to chronological date/time following the most recent scheduled visit.

Table 11 Visit Mappings for Analysis

Protocol/CRF Visit number (VISITNUM)	Protocol/CRF VISIT (VISIT)	Planned time point number/hour (--TPTNUM)	Planned timepoint name /Hour (--TPT)	Analysis Visit Number (AVISITN)	Analysis Visit (AVISIT)	Analysis Timepoint Number (ATPT)	Analysis Timepoint (ATPT)
1	Screening (-30 to -1)	.		1	Screening		
	Unscheduled[1]			1.1	Day 1 (Check-in)[1]		
	Unscheduled[1]			1.2	Pre-First TM BUP[1]		
	Unscheduled[1]			1.3	Post-First TM BUP[1]		
2	Day 1 (Check-in)	.		2	Day 1 (Check-in)		
3	Pre-TM BUP	.		3	Pre-TM BUP		
5	Pre-Sublocade	.		5	Pre-Sublocade		
7	Post-Sublocade	1	1 Hour Post Sublocade Dose	7	Post- Sublocade	1	1 Hour

Protocol/CRF Visit number (VISITNUM)	Protocol/CRF VISIT (VISIT)	Planned time point number/hour (--TPTNUM)	Planned timepoint name /Hour (--TPT)	Analysis Visit Number (AVISITN)	Analysis Visit (AVISIT)	Analysis Timepoint Number (ATPT)	Analysis Timepoint (ATPT)
7	Post-Sublocade	2	2 Hours Post Sublocade Dose	7	Post- Sublocade	2	2 Hours
7	Post-Sublocade	3	3 Hours Post Sublocade Dose	7	Post- Sublocade	3	3 Hours
7	Post-Sublocade	4	4 Hours Post Sublocade Dose	7	Post- Sublocade	4	4 Hours
7	Post-Sublocade	6	6 Hours Post Sublocade Dose	7	Post- Sublocade	6	6 Hours
7	Post-Sublocade	8	8 Hours Post Sublocade Dose	7	Post- Sublocade	8	8 Hours
7	Post-Sublocade	12	12 Hours Post Sublocade Dose	7	Post- Sublocade	12	12 Hours
7	Post-Sublocade	16	16 Hours Post Sublocade Dose	7	Post- Sublocade	16	16 Hours
7	Post-Sublocade	20	20 Hours Post Sublocade Dose	7	Post- Sublocade	20	20 Hours
8	Day 2	24	24 Hours Post Sublocade Dose	8	Day 2	24	24 Hours
8	Day 2	30	30 Hours Post Sublocade Dose	8	Day 2	30	30 Hours

Protocol/CRF Visit number (VISITNUM)	Protocol/CRF VISIT (VISIT)	Planned time point number/hour (--TPTNUM)	Planned timepoint name /Hour (--TPT)	Analysis Visit Number (AVISITN)	Analysis Visit (AVISIT)	Analysis Timepoint Number (ATPT)	Analysis Timepoint (ATPT)
8	Day 2	36	36 Hours Post Sublocade Dose	8	Day 2	36	36 Hours
9	Day 3	48	48 Hours Post Sublocade Dose	9	Day 3	48	48 Hours
10	Day 8	.		10	Day 8		
11	Day 15	.		11	Day 15		
12	Day 22	.		12	Day 22		
13	EOT	.		13	EOT		
14	EOS			14	EOS		

[1]If there are multiple induction doses of TM BUP, the corresponding visits will be slotted in sequential order between the Screening Visit (Analysis Visit 1) and the Day 1 (Check-in) Visit (Analysis Visit 2) for the last induction dose of TM BUP.

6.4 Appendix 4: Definition of Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of the study data or that may significantly impact a subject's rights, safety, or wellbeing.

The important deviations will not be considered in the statistical analyses or in the definitions of analysis populations. All deviations will be listed.

6.5 Appendix 5: Methods to Manage Missing Data

Observed data is used for analysis, unless handling of missing data is described otherwise within the analysis description or in the sections below.

6.5.1 Missing Date Information for Adverse Events

If the AE start date is missing, and the AE stop date is on or after the first dose of study medication, then the AE start date will be imputed as the date of the first dose of study medication.

If the AE start date is missing, and the AE stop date is not missing and before the first dose of study medication, then the AE start date will be imputed as the stop date.

Partial AE Start Date

Missing day and month

- If the year is the same as the year of the date of the first dose of study medication, then the day and month of the date of the first dose of study medication will be assigned to the missing fields.
- If the year is before the year of the date of the first dose of study medication, 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 study medication, 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 study medication, then the day of the first dose of study medication will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of study medication or if both years are the same but the month is before the month of the date of the first

dose of study medication, 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 study medication or if both years are the same but the month is after the month of the date of the first dose of study medication, then the first day of the month will be assigned to the missing day.

If the imputed AE start date is after the AE stop date, then the imputed AE start date will be set to the AE stop date.

6.5.2 Missing Date Information for Concomitant Medications

If the medication start date is missing, and the medication stop date is on or after the first dose of study medication, then the medication start date will be imputed as the date of the first dose of study medication.

If the medication start date is missing, and the medication stop date is not missing and before the first dose of study medication, then the medication start date will be imputed as the medication stop date.

Partial Medication Start Date

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 study medication, then the day and month of the date of the first dose of study medication 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 study medication, 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 study medication, 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 study medication, then the day of the first dose of study medication will be assigned to the missing day.

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

Partial Medication Stop Date

If a medication stop date is missing and the ongoing status is also missing, then the medication is assumed to be ongoing.

If the imputed medication stop date is before the medication start date (whether imputed or non-imputed), then the imputed medication stop date will be equal to the medication 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 study medication, then the day and month of the date of the last dose of study medication 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 study medication, 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 study medication, 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 medication stop date are the same as the month and year of the date of the last dose of study medication, then the day of the last dose of study medication will be assigned to the missing day.

- If either the year is before the year of the date of the last dose of study medication or if both years are the same but the month is before the month of the date of the last dose of study medication, 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 study medication or if both years are the same but the month is after the month of the date of the last dose of study medication, 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 Tests

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table due, for example, to the fact that a character string is reported for a parameter of the numerical type, a derived value will be assigned and used in the statistical analyses. The reported value will be presented in data listings.

The reported and derived values will be assigned prior to DBL and will be noted in the ADaM Reviewer's Guide.

6.7 Appendix 7: Demographic and Baseline Characteristics

Demographic and disease characteristics at screening (age, sex, race, ethnicity, weight, height, BMI, tobacco use, caffeine use and drugs of abuse, baseline disease history (i.e., Screening visit UDS, COWS and OC-VAS)) will be summarised for the subjects who did not enroll, the Enrolled Population, the FAS and the safety analysis set using descriptive statistics.

6.8 Appendix 8: Prior and Concomitant Medications

The definitions for prior and concomitant medications are found in Table 12. The assignments will be made relative to the date/time of first TM BUP dose in the induction phase.

Note that a given medication may be considered both prior and concomitant depending on missing start and end dates/times, under these definitions. Therefore, the prior/concomitant medication categories are not mutually exclusive.

Table 12 Definitions of Prior and Concomitant Medications

End Date/Time of Non-Study Medication	**Start Date/Time of Non-Study Medication**			
	Missing[1]	< Start date/time of Study Medication[2]	≥ Start date/time of Study Medication[2]	
Missing (includes flagged as 'Ongoing')[1]	Prior Concomitant	Prior Concomitant	Concomitant	
< Start date/time of Study Medication[2]	Prior	Prior	**Data Error**	
≥ Start date/time of Study Medication[2]	Prior Concomitant	Prior Concomitant	Concomitant	

[1] If the time is missing, then only the date will be used.

[2]Date/time of first TM BUP dose in the induction phase.

7 REFERENCES

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