Statistical Analysis Plan
for INDV-6000-401 Open-label Induction Sub-study

Protocol Title: A Randomised, Double-Blind Study Comparing 2 Maintenance Dosing Regimens of Buprenorphine Extended-Release Subcutaneous Injection (RBP-6000) in Treatment-Seeking Adult Participants with Opioid Use Disorder and High-risk Opioid Use

Protocol Number: INDV-6000-401

Compound Number: RBP-6000

Short Title: Transform Study: TReating AddictioN in high-risk population with Sublocade FOR Maintenance

Sponsor Name: Indivior Inc.

Legal Registered Address:

10710 Midlothian Turnpike, Suite 125
North Chesterfield, VA 23235
USA

Regulatory Agency Identifier Number(s):

Registry	ID
ClinicalTrials.gov	NCT04995029

Version 3.0 25Aug2023

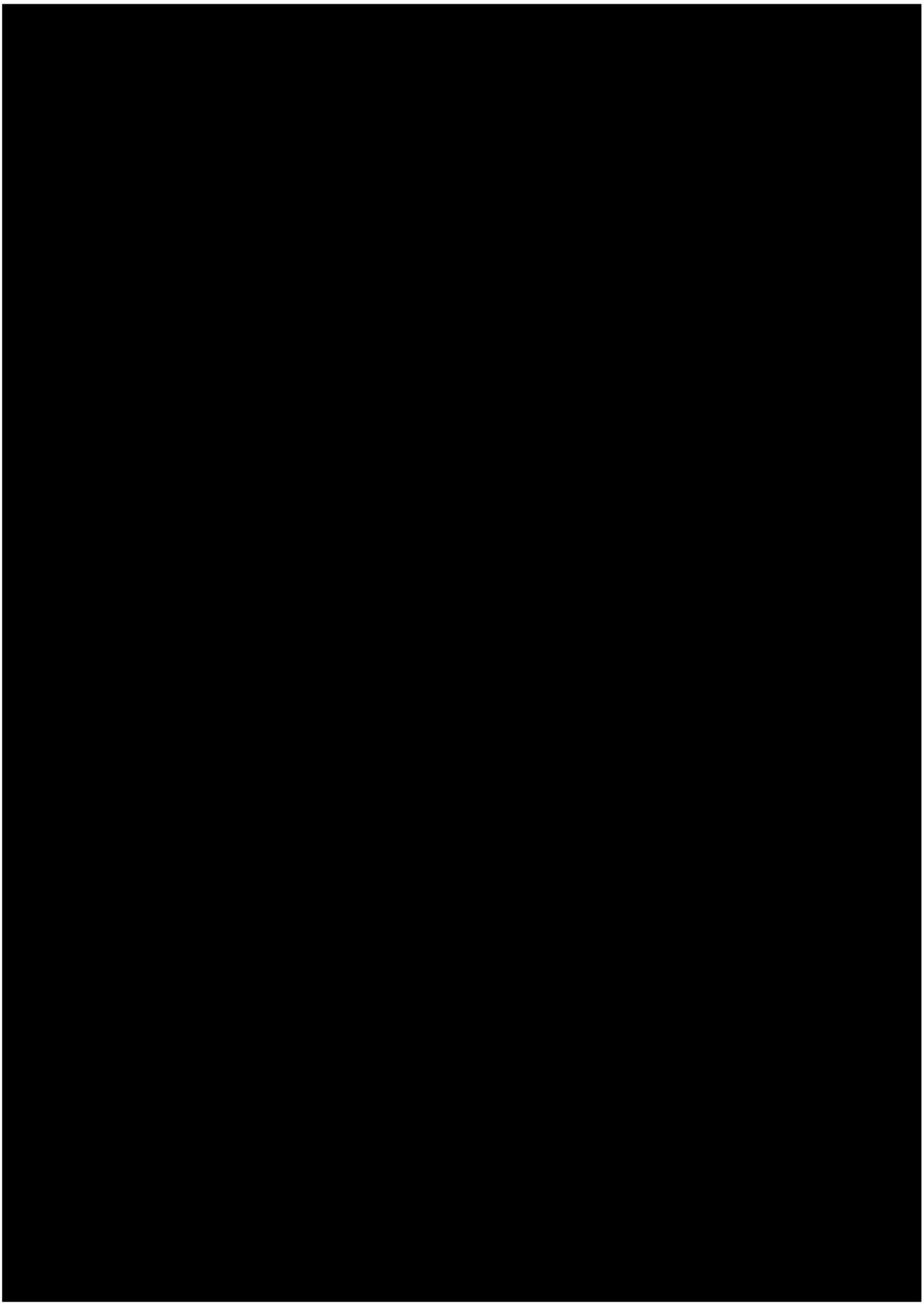


TABLE OF CONTENTS

LIST OF TABLES 5
LIST OF FIGURES 6
1 INTRODUCTION 6
1.1 Version History 6
1.2 Objectives and Endpoints 8
1.3 Study Design 11
2 STATISTICAL HYPOTHESES 12
2.1 Multiplicity Adjustment for the 2 Interim and the Final Analyses 12
3 SAMPLE SIZE AND POWER FOR SUB-STUDY 12
4 POPULATIONS FOR ANALYSIS 13
5 STATISTICAL ANALYSES 15
5.1 General Considerations 15
5.1.1 Analysis Conduct 15
5.1.2 Analysis Conventions 15
5.1.3 Groups for Comparison 16
5.1.4 Open-label Induction Sub-study Period 16
5.1.5 Randomisation Stratification Variable 17
5.2 Participant Dispositions 18
5.2.1 Definitions 18
5.2.2 Analysis of Participant Disposition 18
5.3 Primary Endpoint Analysis 18
5.3.1 Definition of endpoint 19
5.3.2 Main analytical approach 19
5.3.3 Sensitivity Analysis 19
5.4 Secondary Endpoints Analysis 19
5.4.1 Secondary endpoint 1: Time to treatment discontinuation 19
5.4.1.1 Definition of endpoints 20
5.4.1.2 Main analytical approach 20
5.4.1.3 Exploratory analysis approach 20
5.4.2 Secondary endpoints 2 and 3: The proportion of participants reporting adverse events up to Injection 2, and between Injections 2 and 3 20
5.4.2.1 Definition of endpoints 20

5.4.2.2 Main analytical approach 21
5.4.2.3 Supportive Analyses 21
5.5 [redacted]
5.6 Safety Analyses 25
5.6.1 Extent of Exposure 25
5.6.2 Adverse Events 26
5.6.3 Vital Signs 27
5.6.4 Body Weight and BMI 27
5.6.5 Electrocardiograms 28
5.6.6 Liver Function Tests 28
5.6.6.1 Factors of Upper Limit of Normal 28
5.6.6.2 LFT values 29
[redacted]
5.7 Other Analyses 29
5.7.1 Concomitant Medications, Other 29
5.7.2 Induction Attempts 29
5.7.3 UDS Test Results 30
5.7.4 Demographic and Baseline Characteristics 30
[redacted]
5.7.6 Subgroup/Subpopulation analyses 31
5.8 Interim Analyses 31
6 SUPPORTING DOCUMENTATION 32
6.1 Appendix 1: List of Abbreviations 32
6.2 Appendix 2: Changes to Protocol-Planned Analyses 33
6.3 Appendix 3: Schedules of Events 34
6.4 Appendix 4: Methods to Manage Missing Data 34
6.4.1 Missing Date Information for Adverse Events 34
6.4.2 Missing Time Information for Adverse Events 34

6.4.2.1 Partial AE Start Date 34
6.4.3 Missing Date Information for Concomitant Medications 35
6.4.3.1 Partial Medication Start Date 35
6.4.3.2 Partial Medication Stop Date 36
6.4.4 Missing Time Information for Prior/Concomitant Medications 37
[redacted]
6.5 Appendix 5: Prior Medications and Concomitant Medications 37
6.6 Appendix 6: Medical History 38
6.7 Appendix 7: Customised MedDRA Queries 38
6.7.1 Customised MedDRA Query (CMQ) List of Preferred Terms for Drug Related Hepatic Disorders 38
6.7.2 Customised MedDRA Query (CMQ) List of Preferred Terms for Injection Site Reaction 41
6.8 Appendix 8: Derivation of Overall UDS Result for Opioids Use 42
6.8.1 Centrally Tested UDS 42
6.8.2 On-site dipstick UDS 43
7 REFERENCES 43

LIST OF TABLES

Table 1. SAP Version History Summary 6
Table 2. Primary and Secondary Estimands 9
Table 3. 1-Sided Type I Error at Each IA, Final Analysis and Overall, Under Different Null Scenarios for 10% Non-inferiority Margin 12
Table 4. Cumulative Power at 2 Planned Interim Analyses and Final Analysis Under Different Assumptions of Retention Rate at Injection 2 13
Table 5. Populations for Analysis 14
Table 6. Assignment of Treatment Retention at Injection 2 19
Table 7. Interim Analysis: Assignment of Treatment Retention at Injection 2 32
Table 8. List of Abbreviations 32
Table 9. Definitions of Prior and Concomitant Medications 38
Table 10. Customised MedDRA Query (CMQ) List of Preferred Terms for Drug Related Hepatic Disorders 38
Table 11. Customised MedDRA Query (CMQ) List of Preferred Terms for Injection Site Reaction 41

LIST OF FIGURES

Figure 1. Open-label Induction Sub-study Schematic.....17

1 INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the efficacy, safety, and pharmacokinetic data collected in the sub-study of Study INDV-6000-401 based on the protocol amendment 3 dated 07 Apr 2022. This document does not modify the plans outlined in the protocol.

The main study is designed to compare the efficacy, safety, and tolerability of 2 maintenance doses of RBP-6000, 300 mg and 100 mg, administered every 4 weeks, in treatment-seeking participants with moderate to severe opioid use disorder (OUD) and high-risk opioid use (ie, those who use opioids via an injection route and/or use high-dose/potency opioids) that may benefit from the higher 300-mg maintenance dose. The Open-label Induction Sub-study (OLIS) is designed to compare the treatment retention of all participants inducted onto RBP-6000 using Standard of Care (SoC) (minimum 7 days of transmucosal [TM] buprenorphine [BUP] per label) with a more rapid induction (RI) onto RBP-6000 treatment. (Note that in the protocol, the OLIS is referred to as the Open-label Treatment Period in the context of the main study.)

The OLIS and main study Schedules of Events can be found in Section 6.3. The duration of participation in the main study is up to approximately 46 weeks (30 days of screening, ≤2 weeks of open-label induction, 38 weeks of treatment, and 2 weeks of follow-up). The duration of participation in the sub-study is up to approximately 11 weeks (30 days of screening, ≤2 weeks of open-label induction, 5 weeks of treatment).

Specification for tables, listings, and figures (TLFs) will be provided in a separate document.

[redacted]

1.1 Version History

Table 1. SAP Version History Summary

SAP Version	Associated Protocol Amendment	Approval Date	Change	Rationale
1.0	Protocol amendment 3 dated 07 Apr 2022	05 May 2022	Not Applicable	Original version
2.0	Protocol amendment 3 dated 07 Apr 2022	23 Sep 2022	The description of the Evaluable population in Table 5 was	Correction.

Table 1. SAP Version History Summary

SAP Version	Associated Protocol Amendment	Approval Date	Change	Rationale
			updated to match the description in Table 2.	
			[redacted]	[redacted]
			Modifications to text in Table 2, Table 4, and Sections 1.2, 5.1.2, and 5.5.2.	Update or clarification.
3.0	Protocol amendment 3 dated 07 Apr 2022	25Aug2023	Additions in Table 2, Table 5, and Sections 5.1.3, 5.3, and 5.5.	To perform sensitivity analyses for the primary endpoint according to randomised induction groups.
			Additions in Section 5.1.2.	To describe handling of re-screened participants.
			[redacted]	[redacted]
			Additions in Section 5.4.1.2.	To perform KM plots by subpopulation.
			Additions in Section 5.4.2.1.	To define TEAE status when AE onset time is missing.
			[redacted]	[redacted]
			Additions in Section 5.5.3.	To describe the change from Pre-TM BUP analysis, the timepoints for the change from Pre–RBP-6000 timepoint, and the graphical presentations.
			[redacted]	[redacted]
			Additions to Section 5.6.1.	To describe additional summaries and clarify description of some summaries.

Table 1. SAP Version History Summary

SAP Version	Associated Protocol Amendment	Approval Date	Change	Rationale
			Additions in Section 5.6.2.	To clarify analyses descriptions, add 1 category to the TEAE summary, add analysis of Run-in Period.
			Add Sections 5.6.3 through 5.6.7, addition in Section 5.7.1.	To describe analyses of additional parameters that were required for the final analysis.
			Updates in Section 5.7.2.	Update the population for analysis and clarifications.
			Updates in Section 5.7.3 and 5.7.5.	Clarifications of analysis specifications.
			Updates in Section 5.7.6.	Add parameters to be summarised by UDS subpopulation.
			Table 8.	Add abbreviations.
			Update Section 6.2.	Add and clarify changes to planned analyses.
			Update Section 6.4.2, 6.4.4 and 6.4.5	Describe handling of missing data for AEs, prior and concomitant medications, [redacted]

1.2 Objectives and Endpoints

The primary objective of the OLIS is to compare treatment retention of participants following RI or SoC induction onto RBP-6000.

The secondary objective of the sub-study is to evaluate the safety and tolerability of RBP-6000 in participants during the OLIS.

[redacted]

The primary and secondary objectives are presented in Table 2 with their associated estimands.

Table 2. Primary and Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	**Population[a]**	**IES**	**PLS (Analysis)**
Primary Objective: To compare treatment retention of participants following rapid induction or SoC induction onto RBP-6000 with respect to:				
Primary Efficacy Endpoint	Treatment retention at Injection 2, defined as the proportion of participants receiving Injection 2 at the Week 2 Visit among those who received at least 1 dose of TM BUP for induction and did not demonstrate idiosyncratic response to the first dose of TM BUP. Participants who discontinue treatment within the sub-study due to not meeting Inclusion/Exclusion criteria will be excluded.	Evaluable Population for treatment retention/discontinuation	Not applicable: Intercurrent events are not relevant for this endpoint.	Retention rate will be estimated by Bayesian beta-binomial model using non-informative uniform prior, ie, Beta (1,1), within individual induction arms. The posterior distribution of retention rate difference between the 2 arms will be obtained and utilised to calculate the posterior probability of non-inferiority of the RI to SoC induction using a 10% non-inferiority margin or a favourable trend of the RI over the SoC induction. The participants will be analysed corresponding to the induction regimen used ("as treated"[b]).
Primary Efficacy Endpoint/ Sensitivity Analysis	As primary	As primary	As primary	As primary. The participants will be analysed corresponding to the induction arm to which they were randomised ("as randomised"[c]).
Secondary Endpoint 1	Time to treatment discontinuation from the first dose of TM BUP used for induction during the OLIS, defined as the number of days from the first dose of TM BUP from the most recent induction attempt until the last scheduled visit observed during the OLIS.	As primary	Not applicable: Intercurrent events are not relevant for this endpoint.	KM curve presented by the induction arm within the randomisation strata (UDS fentanyl negative vs. positive at the day of first dose of TM BUP) and overall. Participants receiving Injection 3 will be censored administratively at the end of the OLIS; otherwise, participants will be viewed as having discontinued treatment at their last scheduled visit observed during the

Table 2. Primary and Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	**Population[a]**	**IES**	**PLS (Analysis)**
				OLIS. Retention rate (with 95% CI at specific time point) will be estimated using KM product limit method for each induction arm. Hazard ratio (with 95% CI) of RBP-6000 RI to SoC induction will be estimated using a Cox proportional hazard model, with arm as a single covariate, stratified by the randomisation strata.
Secondary Objective: To evaluate the safety and tolerability of RBP-6000 in participants during the OLIS with respect to:				
Secondary Endpoint 2	The proportion of participants reporting adverse events up to Injection 2.	SFAS	While-on-treatment Missing data will not be imputed	Descriptive analysis (n, %)
Secondary Endpoint 3	The proportion of participants reporting adverse events between Injections 2 and 3.	SFAS	While-on-treatment Missing data will not be imputed	Descriptive analysis (n, %)

CI=confidence interval, IES=intercurrent event strategy, KM=Kaplan-Meier, OLIS=Open-label Induction Sub-study, PLS=population level summary, RI=rapid induction, SFAS=sub-study full analysis set, SoC=standard of care, TM=transmucosal, UDS=urine drug screen

a See Section 4 for details.

b Actual arm

c Planned arm

[redacted]

1.3 Study Design

This SAP describes the analysis for the OLIS nested within the main study, which is a randomised, double-blind, parallel group, multicentre study to compare the efficacy, safety, and tolerability of 100mg and 300-mg maintenance doses of RBP-6000 administered every 4 weeks to high-risk, treatment-seeking adult participants with moderate to severe OUD (as assessed by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5]) who use opioids via an injection route and/or use high doses of opioids. The OLIS is designed to compare the treatment retention of all participants inducted onto RBP-6000 using SoC (minimum 7 days of TM BUP per label) with RI onto RBP-6000 treatment.

The OLIS randomisation is implemented using an Interactive Web Response System (IWRS). Participants who meet all of the eligibility criteria and all of the TM BUP dosing criteria are randomised following the first induction day urine drug screen (UDS), at a 2:1 ratio to receive either RI or SoC induction. The induction randomisation number, assigned via the IWRS, used central, blocked, stratified randomisation schedules. The stratification factor is first induction day UDS positive for fentanyl (yes or no). Participants who are randomised but do not receive TM BUP will not be replaced.

The OLIS randomisation schedules were generated using SAS v9.4 using a balanced-across-centres (BAC) approach [Song, 2003]. For the BAC approach, all permuted blocks with specified block size (size=3 with treatment ratio 2:1) were determined. Then the block order was randomly permuted to form a Latin Square, and blocks dynamically allocated to centre at the time of randomisation of the first participant. This approach helps balance the treatment assignments across centres when blocks are left incomplete.

Approximately 489 participants will be enrolled and receive RBP-6000 treatment in the OLIS in order to meet the sample size requirements for the main study.

Two interim analyses (IA) will be performed to allow early declaration of non-inferiority (NI) of RI to SoC induction with respect to treatment retention at Injection 2 (see Section 3 and Section 5.8 for details). If NI is declared at the first IA, then the second IA might not be performed.

2 STATISTICAL HYPOTHESES

For the primary endpoint (treatment retention at Injection 2), the null and alternative statistical hypotheses are:

H_0: retention rate of RI – SoC induction ≤ -10% (NI margin of 10%)

H_A: retention rate of RI – SoC induction > -10%.

The criterion for success (ie, demonstrating NI) at an IA or final analysis is based on the posterior probability of retention rate difference (RI – SoC) > -10%. The NI of RI to the SoC induction will be declared if the posterior probability is higher than 96%. The 96% critical value is chosen so that the overall 1-sided Type I error is less than 10%.

2.1 Multiplicity Adjustment for the 2 Interim and the Final Analyses

Two interim analyses will be performed at N≥120 and N≥240 randomised participants treated with TM BUP (respectively) to allow early declaration of NI of RI to SoC induction with respect to treatment retention at Injection 2 (see Section 5.8 for details). At each IA, the criterion of NI is the posterior probability of retention rate difference (RI – SoC) > -10% being 96% or greater.

A 96% critical value at each IA and the final analysis is chosen to provide overall 1-sided Type I error less than 10%. Table 3 shows 1-sided Type I error at each IA, final analysis and overall, for 5 null hypothesis scenarios for 10% NI margin where the retention rate of RI is truly 10% less than control.

Table 3. 1-Sided Type I Error at Each IA, Final Analysis and Overall, Under Different Null Scenarios for 10% Non-inferiority Margin

	Assumptions of Retention Rate at Injection 2				
Analysis	P_{SoC}=0.65 P_R=0.55	P_{SoC}=0.70 P_R=0.60	P_{SoC}=0.75 P_R=0.65	P_{SoC}=0.80 P_R=0.70	P_{SoC}=0.85 P_R=0.75
IA at n=120	0.0426	0.0439	0.0446	0.0462	0.0467
IA at n=240	0.0258	0.0267	0.0258	0.0263	0.0276
FA at n=489	0.0232	0.0234	0.0237	0.0235	0.0235
Overall	0.0916	0.0941	0.0941	0.0959	0.0978

FA=Final Analysis; IA=Interim Analysis; P_R=retention rate of RI; P_{SoC}=retention rate of SoC induction; SoC=standard of care

Note: A total of 100,000 simulations were performed per scenario.

If NI is declared at the first IA, then the second IA might not be performed. The final analysis will be performed irrespective of the number of IAs.

3 SAMPLE SIZE AND POWER FOR SUB-STUDY

The sample size for the sub-study is based on the required sample size for the main study and the assumed premature discontinuation rate in the sub-study, as the sub-study is an integral

part of the main study. Approximately 489 participants will be randomised in a 2:1 ratio to RI or SoC induction arms. Under the assumption of 70% retention rate at Injection 2 for both arms and with 2 planned IAs at 120 and 240 participants, a total of 489 participants will provide 77.2% power to conclude NI of RI to SoC induction under 10% NI margin. Table 4 provides cumulative power at the 2 planned IAs and the final analysis under different assumptions of retention rate at Injection 2, with scenarios of same retention for both arms or greater retention rate for RI. The assumption about the possible retention rate at Injection 2 was based on the retention rates observed in the 2 previous Phase 3 studies (RB-US-13-0001 and RB-US-13-0003). In these 2 previous Phase 3 studies, among the participants with OUD who initiated SoC induction, about 65.7% (or 72.1%) received their second RBP-6000 injection. For injection route users, the retention rate was about 64.4% (or 70.1%).

Table 4. Cumulative Power at 2 Planned Interim Analyses and Final Analysis Under Different Assumptions of Retention Rate at Injection 2

	Assumptions of Retention Rate at Injection 2				
Analysis	$P_{SoC}=P_R=0.65$	$P_{SoC}=P_R=0.70$	$P_{SoC}=P_R=0.75$	$P_{SoC}=P_R=0.80$	$P_{SoC}=P_R=0.85$
IA at n=120	0.277	0.294	0.324	0.369	0.449
IA at n=240	0.489	0.517	0.564	0.627	0.723
FA at n=489	0.742	0.772	0.817	0.869	0.932
	$P_{SoC}=0.65$ $P_R=0.70$	$P_{SoC}=0.7$ $P_R=0.75$	$P_{SoC}=0.75$ $P_R=0.80$	$P_{SoC}=0.80$ $P_R=0.85$	$P_{SoC}=0.85$ $P_R=0.90$
IA at n=120	0.498	0.538	0.598	0.679	0.804
IA at n=240	0.780	0.816	0.867	0.922	0.974
FA at n=489	0.963	0.976	0.988	0.996	>0.999
	$P_{SoC}=0.65$ $P_R=0.75$	$P_{SoC}=0.70$ $P_R=0.80$	$P_{SoC}=0.75$ $P_R=0.85$	$P_{SoC}=0.80$ $P_R=0.90$	$P_{SoC}=0.85$ $P_R=0.95$
IA at n=120	0.726	0.781	0.844	0.924	0.988
IA at n=240	0.945	0.968	0.986	0.998	>0.999
FA at n=489	0.998	0.999	>0.999	>0.999	>0.999

FA=Final Analysis; IA=Interim Analysis; P_R=retention rate of RI; P_{SoC}=retention rate of SoC Induction; SoC=standard of care

Note: A total of 100,000 simulations were performed per scenario.

4 POPULATIONS FOR ANALYSIS

This section describes the analysis populations for the final analysis. For details on the analysis population for the IA, see Section 5.8.

Table 5. Populations for Analysis

Population	Description
Screened	All participants who sign the informed consent form.
Sub-study Randomised Population (SRP)	The SRP will comprise all participants who give informed consent and are randomised to sub-study treatment. The participants will be analysed corresponding to the induction arm to which they were randomised (ie, planned arm).
Sub-study Full Analysis Set (SFAS)	The SFAS will comprise all participants who are randomised to sub-study treatment and receive the first dose of TM BUP and do not demonstrate idiosyncratic response to the first dose of TM BUP (ie, allergic / hypersensitivity reaction to TM BUP as recorded on the electronic case report form [eCRF] disposition). The participants will be analysed corresponding to the induction arm they received ("as treated", ie, actual arm), given that logistically it is highly unlikely for them to receive the induction arm that they were not randomised to since the randomised arm triggers eCRF forms corresponding to the schedule of events for that arm. Participants who were randomised and inducted with neither RI or SoC (which is a key protocol deviation) will be excluded from the SFAS. The SFAS will serve as the primary population for the analysis in this sub-study.
Evaluable Population for Treatment Retention/Discontinuation[a]	For analysis pertaining to treatment retention and time-to-treatment discontinuation, the SFAS participants who discontinue treatment within the sub-study due to not meeting Inclusion/Exclusion criteria will be also excluded. The participants will be analysed corresponding to the induction arm they received ("as treated", ie, actual arm).
[redacted]	[redacted]

a Note that this population is described in the protocol but was not given a distinct population name. It is named in this statistical analysis plan for ease of reference and clarity in estimand and analysis specifications.

5 STATISTICAL ANALYSES

5.1 General Considerations

5.1.1 Analysis Conduct

The interim and final analyses for the sub-study will be performed using SAS® Version 9.4 or SAS EG Version 7.1 (SAS Institute Inc., Cary, North Carolina, United States of America) on a Unix operating system. The interim analyses will be performed using a snapshot extraction of the relevant electronic case report form (eCRF) and external data as of a specified cut-off date. The interim analyses cut-off dates will be determined based on the interim analysis sample size and population requirements described in Section 5.8. The final analysis also will be performed using a snapshot extraction of the relevant eCRF and external data as of a specified cut-off date. The final analysis cut-off date will be determined after screening has closed for the study and all participants have completed the OLIS. The final analysis will be performed irrespective of the number of IAs.

If NI is declared at the first or second IA and the results of the IA are submitted to regulatory authorities, then all of the endpoints (primary, secondary, [redacted]), participant disposition, baseline demographic characteristics, and disease history will be analysed for inclusion in the interim CSR.

Adverse events (AE) and medical/surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the concomitant medications will be coded using World Health Organization Drug Dictionary. Dictionary versions and additional details of the coding process are described in the Data Management Plan.

5.1.2 Analysis Conventions

For participants who re-screen, only the most recent screening attempt will be included.

Continuous variables will be summarised using descriptive statistics such as mean, standard deviation [SD], median, minimum, and maximum. In addition, geometric mean and coefficient of variation will also be summarised for BUP plasma concentration. Categorical variables will be reported as frequency counts (including number missing) and the percentage of participants in corresponding categories.

Individual participant data will be presented by participant in data listings for the Screened Population unless otherwise specified. Data listings will include all data collected from the initial Screening Visit to Injection 3 Visit (Week 6 Day 36 Visit), including unscheduled and end-of-study visits occurring before reaching Injection 3 (Week 6 Day 36 Visit).

Tables and figures presenting summary data will include scheduled timepoints/visits and assessments only. Figures of individual participant data will include all timepoints/visits, scheduled and unscheduled. Timepoints/visits will be presented chronologically.

Observed data are used for analysis, unless handling of missing data is described otherwise within the analysis description or in Section 6.4.

5.1.3 Groups for Comparison

Data will be summarised by RBP-6000 induction arm: RI and SoC induction, and total (where applicable). The treatment labels will be presented in the TLFs as:

- "RI" for rapid induction
- "SoC" for standard of care induction
- "Total" for all (RI + SoC)

Comparison will be made (where applicable) by RBP-6000 induction arms (RI and SoC induction).

Participants may be analysed corresponding to the induction treatment they received ("as treated", ie, actual arm) or corresponding to the induction treatment to which they were randomised ("as randomised", ie, planned arm), as stated in the analysis populations definitions (Section 4) or in sensitivity analysis sections (Section 5.3.3).

5.1.4 Open-label Induction Sub-study Period

The treatment period for the OLIS begins when the first TM BUP dose is given and ends immediately prior to a participant receiving double-blind RBP-6000 Injection 3. Note that pre-dose assessments for Injection 3 are considered part of the OLIS. See Figure 1 for the OLIS schematic.

For the RI arm, the Induction Day 1 Visit of the most recent induction attempt and the Week 1 Day 1 Visit for the first RBP-6000 injection occur on the same calendar day. In the protocol, this day is the "Day 1" of the RI arm: the RI participants receive their first RBP-6000 injection about 1 hour post TM BUP and then remain on site about 4 hours post injection. The investigator-evaluated PWs occurring within the 1-hour window post TM BUP under Induction Day 1 Visit and those occurring within the 4-hour window post RBP-6000 injection under Week 1 Day 1 Visit are recorded on "Day 1" of the RI arm.

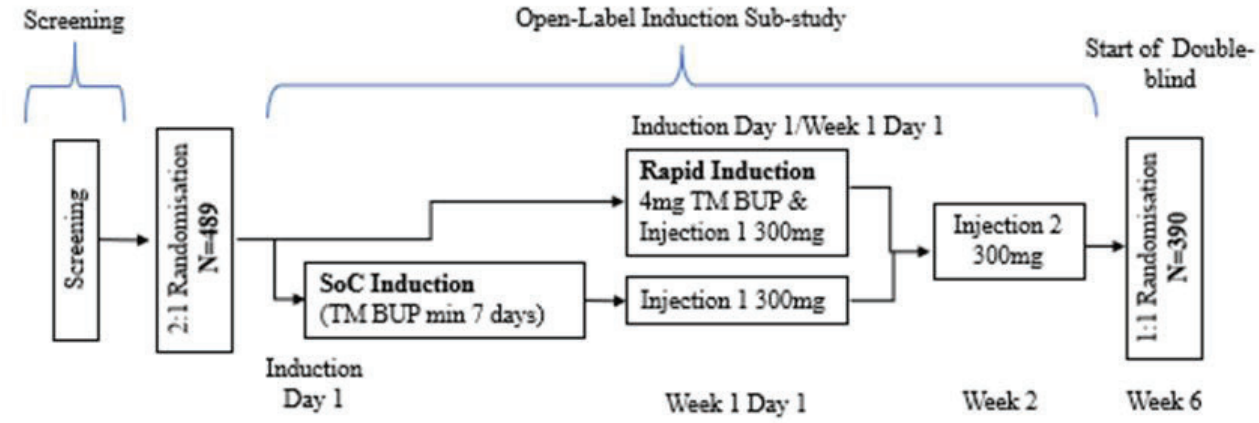
For the SoC arm, the Week 1 Day 1 Visit for the first RBP-6000 injection occurs about 7 to 14 days after the Induction Day 1 Visit. At the Induction Day 1 Visit (of the most recent induction attempt), the SoC participants remain on site about 5 hours after the first TM BUP, to serve as the control period for the 5-hour on-site duration post TM BUP on "Day 1" of the RI arm; at Week 1 Day 1 Visit, the SoC participants remain on site about 4 hours post RBP-6000 injection at Week 1 Day 1 Visit, to serve as the control period for the 4-hr on-site duration post injection on "Day 1" of the RI arm. [redacted]

Therefore, the Induction Day 1 Visit or the Week 1 Day 1 Visit will be used to refer to the "Day 1" of the RI arm, depending on which visit of the SoC arm is to be compared.

Handling of multiple Induction Check-in Days/repeat attempts at induction are described in the analysis sections for the individual endpoints. Example scenarios that may result in multiple Induction Check-in Days/repeated attempts at induction are the following:

- PW from TM BUP that would prevent RBP-6000 administration
- Participant must leave before the in-clinic assessments on an Induction Day Visit are completed

Figure 1. Open-label Induction Sub-study Schematic



BUP=buprenorphine; min=minimum; SoC=standard of care; TM=transmucosal

5.1.5 Randomisation Stratification Variable

The OLIS randomisation is stratified according to the same-day UDS result for fentanyl (negative or positive) on the first induction attempt. The same-day UDS result for fentanyl will be recorded in the eCRF, and the randomisation system will utilise the value recorded at the time of randomisation to assign the randomisation stratum. There is a possibility the incorrect stratum is used for randomisation, in the event the same-day UDS result for fentanyl recorded in the eCRF on the first induction attempt is corrected following randomisation. However, the stratum used for randomisation will be used for analyses involving stratum. See Section 5.7.6 for analyses by fentanyl-positive and fentanyl-negative UDS subpopulations, as defined by the eCRF same-day UDS result for fentanyl on the Induction Day 1 Visit of the most recent induction attempt.

5.2 Participant Dispositions

5.2.1 Definitions

Participant completion and discontinuation from treatment are described in the protocol as follows:

- A completed participant for the OLIS is one who has been randomised and has completed Injection 3, otherwise he/she is considered prematurely discontinued. Note that participants who prematurely discontinue from the OLIS will also prematurely discontinue from the main study.
- A participant will be considered withdrawn from treatment if the participant has permanently discontinued study treatment.

5.2.2 Analysis of Participant Disposition

The number and percentage of participants who were screened and randomised or not randomised, and the reasons for not randomised (ie, discontinued before randomisation), will be summarised for the Screened population. For the SRP and SFAS, the number and percentage of participants who received TM BUP; received RBP-6000 Injections 1, 2, and 3; completed the OLIS (as defined in Section 5.2.1); or discontinued before TM BUP, after TM BUP, before RBP-6000 injection, or after RBP-6000 during the OLIS (and the reasons for discontinuation), will be summarised within randomisation strata and for overall. These participant disposition analyses will be repeated for participants who did and did not experience precipitated withdrawal.

The number and percentage of participants comprising each analysis population (Section 4) will be summarised.

The number and percentage of participants failing entry criteria will be summarised overall and by individual criterion for the Screened population and the SRP.

The number and percentage of participants with important (key) protocol deviations will be summarised overall and by investigator site for the SRP.

The number and percentage of participants who were randomised using the incorrect stratum (ie, the stratum the IWRS used for randomisation does not match the stratum data as collected on the eCRF, see Section 5.1.5) will be summarised for the SRP.

5.3 Primary Endpoint Analysis

Refer to Table 2 for the information on the attributes of the primary estimand. Additional details are provided below.

The analyses of primary endpoint will use the Evaluable Population for treatment retention/discontinuation.

5.3.1 Definition of endpoint

Treatment retention at Injection 2 is defined as the proportion of participants receiving Injection 2 at the Week 2 Visit among those in the Evaluable Population for treatment retention/discontinuation.

The analysis value (Yes/No) for treatment retention at Injection 2 for each participant is assigned as described in Table 6 for the Evaluable Population for treatment retention/discontinuation.

Table 6. Assignment of Treatment Retention at Injection 2

Participant status	Treatment Retention at Injection 2
Received Injection 2 at Week 2 (nominal) Visit	Yes
Missed Injection 2 at Week 2 (nominal) Visit but received Injection 3 at Week 6 Day 36 Visit	Yes
Otherwise	No

5.3.2 Main analytical approach

The treatment retention rate at Injection 2 will be estimated by Bayesian beta-binomial model using non-informative uniform prior, ie, Beta (1,1), within individual induction arms. The posterior distribution of retention rate difference between the 2 arms will be obtained and utilised to calculate the posterior probability of NI of the RI to SoC induction using a 10% NI margin or a favourable trend of the RI over the SoC induction.

The criterion for success (ie, demonstrating NI) is based on the posterior probability of retention rate difference (RI – SoC) greater than -10%. The NI of RI will be declared if the posterior probability is at 96% or greater. If the NI of RI to SoC is declared, the posterior possibility of retention rate difference (RI – SoC) greater than 0 will be estimated to evaluate the superiority of RI over SoC induction.

5.3.3 Sensitivity Analysis

The analysis will be repeated, except participants will be analysed as per the randomised treatment (ie, planned arm).

5.4 Secondary Endpoints Analysis

Refer to Table 2 for the information on the attributes of the secondary estimands. Additional details are provided below.

5.4.1 Secondary endpoint 1: Time to treatment discontinuation

The analysis of secondary endpoint 1 will use the Evaluable Population for treatment retention/discontinuation.

5.4.1.1 Definition of endpoints

This analysis will utilise the most recent induction attempt. The time from the first dose of TM BUP to treatment discontinuation will be calculated in days as the date of the last scheduled visit observed during the OLIS minus the date of the first dose of TM BUP (for the most recent induction) +1. Participants receiving RBP-6000 Injection 3 will be censored administratively at the end of the OLIS, and the corresponding censor time will be calculated as the date of Injection 3 minus the date of the first dose of TM BUP +1.

The population for analysis (ie, the at-risk population at time 0) will be the Evaluable Population for treatment retention/discontinuation.

5.4.1.2 Main analytical approach

The time from the first dose of TM BUP to treatment discontinuation will be presented by induction arm using Kaplan-Meier (KM) curves within the randomisation strata (UDS fentanyl negative vs. positive at the day of first dose of TM BUP) and for overall. Retention rate (with 95% confidence interval [CI]) at 5 weeks (35 days) will be estimated using KM product limit method for each induction arm within the randomisation strata and for overall. Hazard ratio (with 95% CI) of RBP-6000 RI to SoC induction will be estimated using a Cox proportional hazard model, with treatment arm as a single covariate, stratified by the randomisation strata. KM plots by treatment arm and by treatment arm and fentanyl UDS subpopulation will be produced.

5.4.1.3 Exploratory analysis approach

The completion rate for the OLIS (ie, receiving double-blind RBP-6000 Injection 3) will be estimated by Bayesian beta-binomial model using non-informative uniform prior, ie, Beta (1,1), within individual induction arms. The posterior distribution of completion rate difference between the 2 arms will be obtained and presented in a similar way as the primary endpoint, treatment retention rate at injection 2.

5.4.2 Secondary endpoints 2 and 3: The proportion of participants reporting adverse events up to Injection 2, and between Injections 2 and 3

The analysis of secondary endpoints 2 and 3 will use the SFAS.

5.4.2.1 Definition of endpoints

These endpoints will encompass all induction attempts, and therefore utilise the first dose of TM BUP for derivations. A treatment-emergent adverse event (TEAE) is defined as an AE having an onset date/time after administration of the first TM BUP dose and before the date/time of Injection 3. The TEAEs are classified into the 2 consecutive time intervals, defined as:

- TEAEs up to RBP-6000 Injection 2 are TEAEs with a start date/time on or after the first dose of TM BUP and before the date/time of Injection 2

- TEAEs between RBP-6000 Injections 2 and 3 are TEAEs with a start date/time on or after Injection 2 and before the date/time of Injection 3

Note: If AE onset time is missing, then only the onset date will be used to assign TEAE status. An AE onset date on or after the date of the administration of the first dose of TM BUP will be considered a TEAE.

For participants who received Injections 1 and 3 (but not Injection 2), their TEAE with start date before the date of Injection 3 will be classified into the time interval of "up to RBP-6000 Injection 2". For discontinued participants whose last injection was Injection 1, their TEAE with start date after the last injection will be classified into the time interval of "up to RBP- 6000 Injection 2". For discontinued participants whose last injection was Injection 2, their TEAE with start date after the last injection will be classified into the time interval of "between RBP-6000 Injections 2 and 3".

5.4.2.2 Main analytical approach

The number and proportion of participants with at least 1 TEAE, treatment-related TEAE, serious TEAE, fatal TEAE, serious TEAE meeting LFT criteria, severe TEAE, TEAE leading to discontinuation, or TEAE reported as adverse events of special interest, drug-related hepatic disorders (see definition in Section 6.7.1), injection site reactions (see definition in Section 6.7.2), opioid withdrawal symptoms, and precipitated withdrawal symptoms (per eCRF) will be summarised for each endpoint, by induction arm within randomisation strata and for overall.

The numerator of the proportion for each endpoint will be the number of participants with at least 1 TEAE of interest in the respective time interval. The denominator for endpoint 2 (TEAEs up to RBP-6000 Injection 2) will be the number of participants in the SFAS population. The denominator for endpoint 3 (TEAEs between RBP-6000 Injections 2 and 3) will be the number of the participants in the SFAS population who received Injection 2.

5.4.2.3 Supportive Analyses

The number and percentage of participants reporting TEAEs, reporting TEAEs of opioid withdrawal symptoms (per eCRF), or reporting TEAEs leading to TM BUP dose increase by induction arm within randomisation strata and for overall will be tabulated by System Organ Class (SOC) and Preferred term (PT) for the 2 time intervals, separately.

5.5 Exploratory Endpoint(s) Analysis

The analyses of exploratory endpoints will use the SFAS.

[redacted]

[redacted]

[redacted]

[redacted]

5.5.3 COWS Scores

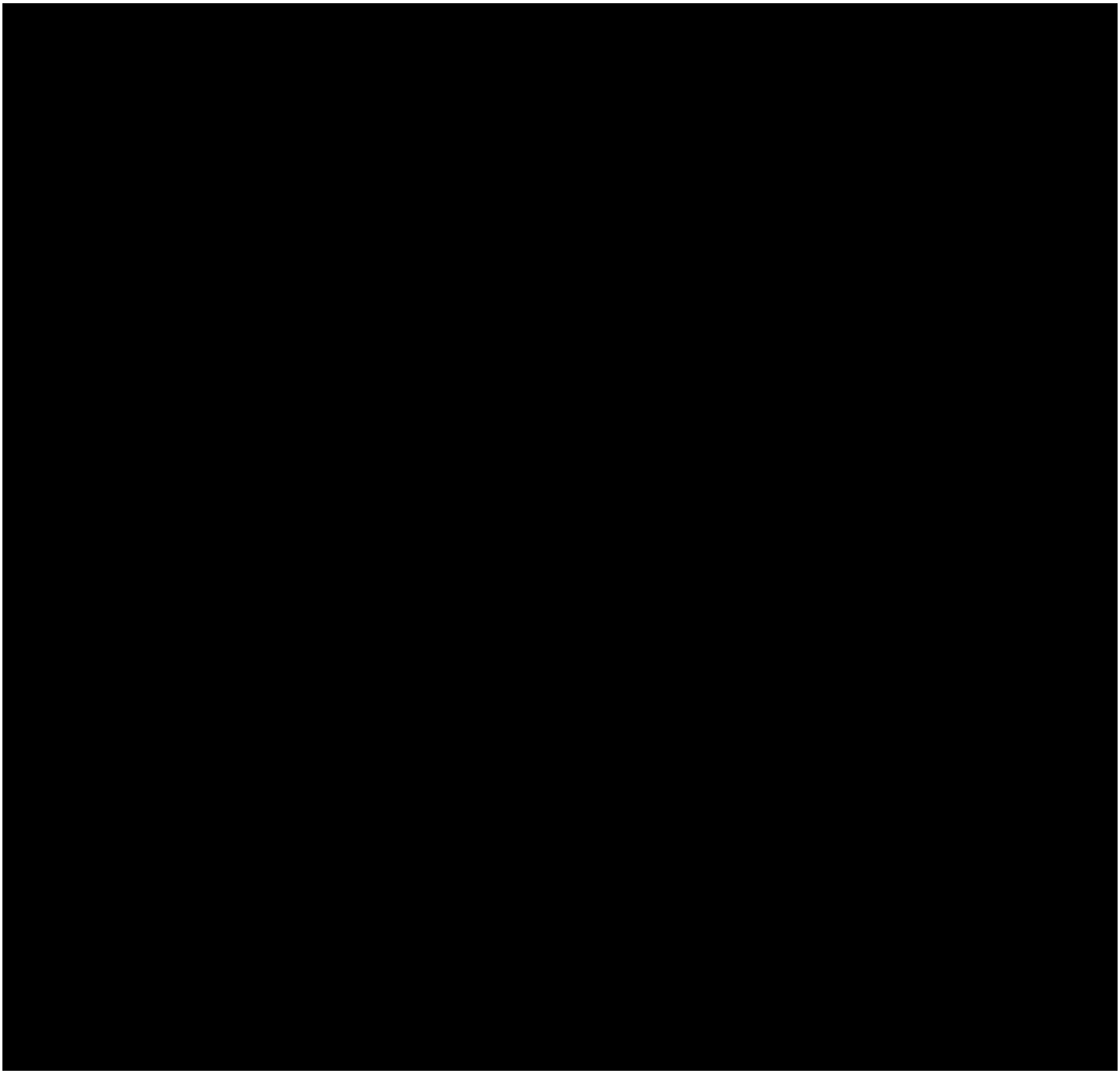
The COWS scores at Screening, pre-TM BUP, and the nominal timepoints during the 5 hours post-TM BUP on the most recent induction day will be summarised overall, by induction arm, [redacted] within individual randomisation strata using descriptive statistics. The change in COWS scores from the pre-TM BUP timepoint to the subsequent nominal timepoints will be summarised in the same manner, and categorically. The timepoints will be aligned across the treatment arms according to the nominal elapsed time from the dose of TM BUP. In addition, the mean difference (RI – SoC) with 95% CI will be presented by each timepoint overall and within each randomisation stratum.

The COWS scores at the pre-dose RBP-6000 timepoint, post RBP-6000 timepoints at Week 1 Day 1 Visit (ie, at 1, 2, and 4 hours post RBP-6000 Injection 1 using nominal timepoints), and subsequent timepoints to the end of the OLIS will be summarised overall, by induction arm [redacted] within individual randomisation strata using descriptive statistics. The change in COWS scores from the pre–RBP-6000 timepoint to the subsequent nominal timepoints will be summarised in the same manner, and categorically. In addition, the mean difference (RI – SoC) with 95% CI will be presented by each timepoint overall and within each randomisation stratum.

The mean COWS scores and mean change scores from the pre-TM BUP timepoint will be plotted by treatment arm, by treatment arm and fentanyl UDS subpopulation, [redacted] for the timepoints during the first 5 hours of the most recent induction day. The mean COWS scores and mean change scores from the pre–RBP-6000 injection timepoint will be plotted by treatment arm, by treatment arm and fentanyl UDS subpopulation, [redacted]

The individual COWS scores of all participants at the corresponding timepoints and visits (described in the previous paragraph) will be presented via a spaghetti plot, distinguished by [redacted] treatment arm within fentanyl UDS subpopulation.

[redacted]



5.6 Safety Analyses

5.6.1 Extent of Exposure

The extent of exposure analyses will be performed for the SFAS using descriptive statistics.

For both treatment arms, the following summaries will be performed:

- Total number of RBP-6000 injections received in the OLIS (ie, 0-3)

- Number of participants who received RBP-6000 at each injection (Injections 1 through 3)
- Total number of induction attempts
- Total dose of TM BUP on the most recent induction day
- Total dose of additional (post-injection) TM BUP during the first 5 hours of the most recent induction day

For the RI arm, the following summaries will be performed:

- the total dose of pre-injection TM BUP on the most recent induction day.
- the time elapsed between TM BUP and Injection 1 on the most recent induction day, overall [redacted]

For the SoC arm, the following summaries will be performed for the participants who received RBP-6000 injection:

- The number of days of dose stabilisation (ie, number of days of SoC Induction with TM BUP prior to the first injection of RBP-6000). The number of days will be calculated as the date of the first dose of TM BUP minus the date of the last dose of TM BUP plus 1. A categorical data summary using categories <7, 7, 8, and >8 will be performed, as well as a continuous data summary.
- The average daily TM BUP dose during the SoC induction phase, calculated as the total cumulative dose divided by the number of days of dose stabilisation.
- The total TM BUP dose on the day prior to first injection of RBP-6000 (Day -1, as collected on the eCRF).

Participants who take TM BUP after Week 1 Day 1 will be presented in a data listing. Use of TM BUP after Week 1 Day 1 is prohibited per the protocol, but if it occurs, the information would be captured on the concomitant medication form of the eCRF.

5.6.2 Adverse Events

The analysis of AEs will use the SFAS.

The investigator determines the intensity of AEs and the relationship of AEs to study medication. In tabular summaries, TEAEs will be sorted by descending percentage in all participants. TEAEs will be summarised overall, by induction arm, and within individual randomisation strata.

The number and percentage of participants reporting TEAEs will be tabulated overall by SOC and PT, by PT, and by severity, SOC, and PT. If more than 1 TEAE is coded to the same PT for the same participant, the participant will be counted only once for that PT using the most severe occurrence for the summarisation by severity.

In addition, the following categories of TEAEs will be tabulated:

- Severe, by SOC and PT
- Serious, by SOC and PT
- Serious AE meeting the criterion “Laboratory values of ALT or AST >3×ULN and bilirubin >2×ULN”, by PT
- Fatal, by PT
- Adverse events of special interest, by PT
- Drug-related Hepatic Disorders and Injection Reaction Events, per the customised MedDRA Query (CMQ) definitions (see Section 6.7), by SOC and PT
- Related to TM BUP, by SOC and PT
- Related to RBP-6000, by SOC and PT
- Leading to treatment discontinuation from TM BUP (action taken is “Drug withdrawn” per eCRF), by SOC and PT
- Leading to treatment discontinuation from RBP-6000 (action taken is “Drug withdrawn” per eCRF), by SOC and PT
- Reported as opioid withdrawal symptom, by SOC and PT
- [redacted]

The number and percent of participants with at least 1 event in the above categories will be presented on an AE summary table.

For the SoC arm, the number and percentage of participants reporting TEAEs during the Run-in Period (TEAEs with a start date on or after the first dose of TM BUP and before the datetime of Injection 1) will be tabulated overall by SOC and PT.

5.6.3 Vital Signs

The vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate), at each nominal scheduled visit, using the most recent induction attempt, will be summarised overall, by induction arm, and within individual randomisation strata at each visit for the SFAS.

Data collection of body temperature was allowed by methods axial, forehead, oral, or ear. Since temperatures may vary somewhat by method, the temperature data will only be listed.

5.6.4 Body Weight and BMI

The results of scheduled assessments of body weight and BMI will be summarised overall, by induction arm, and within individual randomisation strata at each nominal visit for the SFAS.

5.6.5 Electrocardiograms

At each nominal scheduled visit using the most recent induction attempt, electrocardiogram (ECG) numeric variables (heart rate, PR interval, QRS duration, QT Interval, and QT interval corrected using Fridericia's method, QTcF, change from screening for QTcF) will be summarised overall, by induction arm, and within individual randomisation strata for the SFAS. In addition, the number and percentage of participants with QTcF >500 msec and with the QTcF change from Screening to each nominal scheduled visit >60 msec will be summarized overall, by induction arm, and within individual randomisation strata for the SFAS.

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

5.6.6 Liver Function Tests

The following liver functions tests (LFTs) will be collected according to the protocol schedule of events: alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, total protein, gamma glutamyl transferase, and lactase dehydrogenase. Analysis of LFTs will use the SFAS.

5.6.6.1 Factors of Upper Limit of Normal

The number and percentage of participants meeting liver function test criteria for ALT, AST, and total bilirubin during the timeframe after the first dose of TM BUP up to and including Week 6 will be summarised overall, by induction arm, and within individual randomisation strata. For each lab parameter, the participant will be counted only once according to their worst case (highest) result during the timeframe. The criteria are factors of upper limit of normal (ULN), as follows:

a. ALT (>3×ULN)
    - >=8×ULN
    - >=5×ULN to <8×ULN
    - >3×ULN to <5×ULN
b. AST (>3×ULN)
    - >=8×ULN
    - >=5×ULN to <8×ULN
    - >3×ULN to <5×ULN
c. Total Bilirubin (>2×ULN)
    - >=5×ULN

- >2×ULN to <5×ULN

The LFT data will be listed for participants with values meeting these criteria.

5.6.6.2 LFT values

At each nominal scheduled visit using the most recent induction attempt, LFT results and the change in LFT result from screening will be summarised overall, by induction arm, and within individual randomisation strata.

[redacted]

5.7 Other Analyses

5.7.1 Concomitant Medications, Other

The number and percentage of participants taking any concomitant medication during the time period from the first dose of TM BUP up to Injection 2 will be summarised by pharmacological group (ATC level 3) and preferred drug name for the SFAS overall and by induction arm overall and within individual randomisation strata using descriptive statistics. These analyses will include concomitant medications from all induction attempts that have a start date/time before the date/time of Injection 2.

The number and percentage of participants taking any prior medications and concomitant medications (Section 6.5) will be summarised by pharmacological group (ATC level 3) and preferred drug name for the SFAS overall and by induction arm overall and within individual randomisation strata using descriptive statistics.

5.7.2 Induction Attempts

The number and percentage of participants who have multiple induction attempts will be summarised using the SFAS and descriptive statistics. The numerator will be the number of participants with >1 Induction Day 1 Visit, and the denominator will be the number of participants in the SFAS.

The number and percentage of participants who did not continue with an induction attempt, and the reasons for not continuing (as collected in the eCRF) will be summarised using the SRP and descriptive statistics. The numerator will be the number of participants with at least

1 induction attempt that was not continued and the reason for not continuing, respectively, and the denominator will be the number of participants in the SFAS and the number of attempts not continued, respectively. The summaries will be repeated for those participants who were randomised but discontinued before receiving Injection 1.

5.7.3 UDS Test Results

See Section 6.8 for derivation of UDS test results.

Positive results of UDS at Screening, Induction Day 1 (of all induction attempts), Week 1 Day 1, and Weeks 2 through 6 (nominal visits) will be summarised for opiates/morphine, fentanyl, BUP (Screening Visit and first Induction Day 1 attempt only), methadone, and opioids (overall) for the SFAS overall and by induction arm, using observed data and descriptive statistics (number and percent of participants). Positive results for other non-opioid drug substances tested will be summarized in a similar manner.

The denominator for the summary of each UDS test will be the number of participants who have a non-missing result for that test.

5.7.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics (age, sex, race, ethnicity, childbearing potential, weight, height, body mass index, alcohol use, nicotine use, xanthine/caffeine use) and disease history (the randomisation strata, the UDS fentanyl result at the most recent Induction Day 1 Visit, medication for OUD, inclusion criterion 5a/5b met) at Screening will be summarised for the SFAS using descriptive statistics.

[redacted]

5.7.6 Subgroup/Subpopulation analyses

The following analyses will be repeated for the fentanyl-positive and fentanyl-negative subpopulations, as defined by the eCRF same-day UDS result for fentanyl on the Induction Day 1 Visit of the most recent induction attempt.

- Primary endpoint (Section 5.3)
- Secondary endpoints (Section 5.4)
- [redacted]
- AEs (Section 5.6.2)
- Concomitant medications (Section 5.5.2)
- COWS (Section 5.5.3)
- UDS results
- Participant disposition
- Demographic and baseline characteristics
- Exposure

Analyses of the primary endpoint (Section 5.3) will be repeated for the following subpopulations.

- [redacted]
- Participants who are randomised and inducted with neither RI or SoC (which is a key protocol deviation).

5.8 Interim Analyses

Two interim analyses of the primary endpoint (treatment retention at Injection 2) will be performed when all of the first 120/240 (at a minimum) participants who received TM BUP have either (1) received Injection 3, or (2) discontinued prior to Injection 3 (ie, they have completed the early termination visit or they have been discontinued per the eCRF disposition page). The interim analyses will be performed to allow early declaration of noninferiority of RI to SoC induction with respect to treatment retention at Injection 2. At each IA, the criterion of NI is the posterior probability of retention rate difference (RI – SoC) > -10% being 96% or greater. See Section 2.1 and Table 3 for information on the 1-sided Type I error at each IA, final analysis and overall.

Indivior study team personnel will perform the IA(s).

If NI is declared at the first or second IA, then the results will be shared within Indivior:

- A decision will be made whether to submit the results of the IA to regulatory authorities.
- If the results of the IA will be submitted to regulatory authorities, then all of the endpoints (primary, secondary, [redacted]), BUP plasma concentrations, participant disposition, and baseline demographics and disease history will be analysed for inclusion in the interim CSR.

If NI is declared at the first IA, then the second IA might not be performed.

If NI is not declared at the first or second IA, then there will not be any additional secondary [redacted] analyses performed until the final analysis.

The analysis population for the IA is the Evaluable Population for Treatment Retention/Discontinuation, applied to the first 120/240 (at a minimum) participants defined above. Similarly, if analyses for an interim CSR will be performed, the analysis populations will be those noted for the final analysis, applied to the first 120/240 (at a minimum) participants defined above.

At an IA, the value of treatment retention at Injection 2 for each participant is assigned as Yes/No as described in Table 7.

Table 7. Interim Analysis: Assignment of Treatment Retention at Injection 2

Participant status	Treatment Retention at Injection 2
Received Injection 2 at Week 2 (nominal) Visit	Yes
Missed Injection 2 at Week 2 (nominal) Visit but received Injection 3 at Week 6 Day 36 Visit	Yes
Did not receive Injection 2 and discontinued prior to receiving Injection 3 (ie, they have completed the early termination visit or they have been discontinued per the eCRF disposition page and have no RBP-6000 administration data indicating receipt of Injection 2 or 3)	No
Missed Injection 2 at Week 2 (nominal) Visit, have not received Injection 3 at Week 6 Day 36 Visit, and the study disposition status has not been captured in the eCRF	No (imputed)

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1: List of Abbreviations

Table 8. List of Abbreviations

Abbreviation	Term
AE	adverse event
ALQ	above the limit of quantitation
ALT	alanine aminotransferase
AST	aspartate aminotransferase

Table 8. List of Abbreviations

Abbreviation	Term
ATC	Anatomic Therapeutic Chemical
[redacted]	[redacted]
BUP	buprenorphine
CI	confidence interval
COWS	Clinical Opiate Withdrawal Scale
eCRF	electronic case report form
FA	final analysis
IA	interim analysis
IES	intercurrent event strategy
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LFT	liver function tests
MedDRA	Medical Dictionary for Regulatory Activities
NI	non-inferiority
[redacted]	[redacted]
OLIS	Open-label Induction Sub-study
OUD	opioid use disorder
[redacted]	[redacted]
PLS	population level summary
PT	preferred term
[redacted]	[redacted]
QTcF	QT interval corrected using Fridericia's method
RI	Rapid Induction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
[redacted]	[redacted]
SRP	Sub-study Randomised Population
SFAS	Sub-study Full Analysis Set
SoC	standard of care
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TLFB	TimeLine Follow Back
TLF	tables, listings, and figures
TM	transmucosal
UDS	urine drug screen
ULN	upper limit of normal

6.2 Appendix 2: Changes to Protocol-Planned Analyses

The following are changes to the protocol-planned analyses:

- The Sub-study enrolled population (SEP) was renamed as the Sub-study Randomised Population (SRP), as this name better describes the population.

- Some analyses using the SFAS will be repeated whereby the participants will be analysed corresponding to the treatment to which they were randomized ("as randomised", ie, planned arm).
- An exploratory analysis approach for the Secondary Endpoint 1, Time to Treatment Discontinuation was added.
- Only the UDS results will be summarised. The results from the TimeLine Follow Back (TLFB), alone and combined with the UDS were specified in the protocol but are not necessary to meet the objectives of the sub-study. These analyses will be performed for the main study.
- [redacted]
- A categorical summary of change in COWS scores was added.
- For exposure analyses, a summary of the time elapsed between TM BUP and Injection 1 for the RI group was added.
- Analyses of vital signs, ECGs and LFTs were added.

6.3 Appendix 3: Schedules of Events

The Schedules of Events can be found in the protocol.

6.4 Appendix 4: Methods to Manage Missing Data

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

6.4.1 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.

6.4.2 Missing Time Information for Adverse Events

If the AE start or end time is missing, it will not be imputed.

6.4.2.1 Partial AE Start Date

6.4.2.1.1 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 31 December 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 01 January will be assigned to the missing fields.

6.4.2.1.2 Missing month only

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

6.4.2.1.3 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.

6.4.3 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.

6.4.3.1 Partial Medication Start Date

6.4.3.1.1 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 31 December 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 01 January will be assigned to the missing fields.

6.4.3.1.2 Missing month only

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

6.4.3.1.3 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.

6.4.3.2 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.

6.4.3.2.1 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 31 December 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 01 January will be assigned to the missing fields.

6.4.3.2.2 Missing month only

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

6.4.3.2.3 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.

6.4.4 Missing Time Information for Prior/Concomitant Medications

If the start or end time is missing, it will not be imputed.

[redacted]

6.5 Appendix 5: Prior Medications and Concomitant Medications

The definitions for prior and concomitant medications for the sub-study are found in Table 9. The assignments will be made relative to the date/time of the first dose of TM BUP.

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 9. Definitions of Prior and Concomitant Medications

End Date/Time of Non-Study Medication	Start Date/Time of Non-Study Medication			
	Missing[a]	< Start date/time of Study Medication[b]	≥ Start date/time of Study Medication[b] and <end date/time of study medication[b]	≥ end date/time of study medication[b]
Missing (includes flagged as 'Ongoing')[a]	Prior Concomitant	Prior Concomitant	Concomitant	Not a sub-study medication
< Start date/time of Study Medication[b]	Prior	Prior	Data Error	Data Error
≥ Start date/time of Study Medication[b]	Prior Concomitant	Prior Concomitant	Concomitant	Data Error

a If the time is missing, then only the date will be used. See Section 6.4.3 for handling of missing date information

b Study medication includes both TM BUP and RBP-6000, start date/time of study medication is the date/time of first dose of TM BUP in the induction phase, end date/time of study medication is the date/time of the last administration of TM BUP or RBP-6000 (injection 1,2, or 3), whichever is the last.

6.6 Appendix 6: Medical History

The number and percentage of participants reporting medical history events will be tabulated by SOC and PT, by decreasing frequency, for the SFAS using descriptive statistics and observed data.

6.7 Appendix 7: Customised MedDRA Queries

The CMQs included below are based on MedDRA v24.1. These terms will be reviewed against the version of MedDRA used for reporting (see Section 5.1.1), and updated if needed.

6.7.1 Customised MedDRA Query (CMQ) List of Preferred Terms for Drug Related Hepatic Disorders

Table 10. Customised MedDRA Query (CMQ) List of Preferred Terms for Drug Related Hepatic Disorders

Cholestasis and jaundice of hepatic origin	
Bilirubin excretion disorder	Jaundice
Cholaemia	Jaundice cholestatic
Cholestasis	Jaundice hepatocellular
Cholestatic liver injury	Mixed liver injury
Cholestatic pruritus	Ocular icterus
Drug-induced liver injury	Parenteral nutrition associated liver disease
Hepatitis cholestatic	Deficiency of bile secretion
Hyperbilirubinaemia	Yellow skin
Icterus index increased	
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	
Acute hepatic failure	Liver and small intestine transplant

Table 10. Customised MedDRA Query (CMQ) List of Preferred Terms for Drug Related Hepatic Disorders

Acute on chronic liver failure	Liver dialysis
Acute yellow liver atrophy	Liver disorder
Ascites	Liver injury
Asterixis	Liver operation
Bacterascites	Liver transplant
Biliary cirrhosis	Lupoid hepatic cirrhosis
Biliary cirrhosis primary	Minimal hepatic encephalopathy
Biliary fibrosis	Mixed liver injury
Cholestatic liver injury	Nodular regenerative hyperplasia
Chronic hepatic failure	Non-alcoholic fatty liver
Coma hepatic	Non-alcoholic steatohepatitis
Cryptogenic cirrhosis	Non-cirrhotic portal hypertension
Diabetic hepatopathy	Oedema due to hepatic disease
Drug-induced liver injury	Oesophageal varices haemorrhage
Duodenal varices	Peripancreatic varices
Gallbladder varices	Portal fibrosis
Gastric variceal injection	Portal hypertension
Gastric variceal ligation	Portal hypertensive enteropathy
Gastric varices	Portal hypertensive gastropathy
Gastric varices haemorrhage	Portal vein cavernous transformation
Hepatectomy	Portal vein dilatation
Hepatic atrophy	Porto pulmonary hypertension
Hepatic calcification	Renal and liver transplant
Hepatic cirrhosis	Retrograde portal vein flow
Hepatic encephalopathy	Reye's syndrome
Hepatic encephalopathy prophylaxis	Reynold's syndrome
Hepatic failure	Splenic varices
Hepatic fibrosis	Splenic varices haemorrhage
Hepatic hydrothorax	Steatohepatitis
Hepatic infiltration eosinophilic	Subacute hepatic failure
Hepatic lesion	Varices oesophageal
Hepatic necrosis	Varicose veins of abdominal wall
Hepatic steato-fibrosis	Anorectal varices
Hepatic steatosis	Anorectal varices haemorrhage
Hepatitis fulminant	Intrahepatic portal hepatic venous fistula
Hepatobiliary disease	Peritoneovenous shunt
Hepatocellular foamy cell syndrome	Portal shunt
Hepatocellular injury	Portal shunt procedure
Hepatopulmonary syndrome	Small-for-size liver syndrome
Hepatorenal failure	Spider naevus
Hepatorenal syndrome	Splenorenal shunt
Hepatotoxicity	Splenorenal shunt procedure
Intestinal varices	Spontaneous intrahepatic portosystemic venous shunt
Intestinal varices haemorrhage	Stomal varices

Table 10. Customised MedDRA Query (CMQ) List of Preferred Terms for Drug Related Hepatic Disorders

Varicose vein	
Hepatitis, non-infectious	
Acute graft versus host disease in liver	Hepatitis fulminant
Allergic hepatitis	Hepatitis toxic
Autoimmune hepatitis	Ischaemic hepatitis
Chronic graft versus host disease in liver	Lupus hepatitis
Chronic hepatitis	Non-alcoholic steatohepatitis
Graft versus host disease in liver	Radiation hepatitis
Hepatitis	Steatohepatitis
Hepatitis acute	Granulomatous liver disease
Hepatitis cholestatic	Liver sarcoidosis
Hepatitis chronic active	Portal tract inflammation
Hepatitis chronic persistent	
Liver related investigations, signs and symptoms	
Alanine aminotransferase abnormal	Hypercholia
Alanine aminotransferase increased	Hypertransaminasaemia
Ammonia abnormal	Kayser-Fleischer ring
Ammonia increased	Liver function test abnormal
Ascites	Liver induration
Aspartate aminotransferase abnormal	Liver palpable
Aspartate aminotransferase increased	Liver scan abnormal
Bacterascites	Liver tenderness
Bile output abnormal	Mitochondrial aspartate aminotransferase increased
Bile output decreased	Molar ratio of total branched-chain amino acid to tyrosine
Biliary ascites	Oedema due to hepatic disease
Bilirubin conjugated abnormal	Perihepatic discomfort
Bilirubin conjugated increased	Retrograde portal vein flow
Bilirubin urine present	Total bile acids increased
Biopsy liver abnormal	Transaminases abnormal
Blood bilirubin abnormal	Transaminases increased
Blood bilirubin increased	Ultrasound liver abnormal
Blood bilirubin unconjugated increased	Urine bilirubin increased
Bromosulphthalein test abnormal	X-ray hepatobiliary abnormal
Child-Pugh-Turcotte score abnormal	5'nucleotidase increased
Child-Pugh-Turcotte score increased	Blood alkaline phosphatase abnormal
Computerised tomogram liver	Blood alkaline phosphatase increased
Foetor hepaticus	Blood cholinesterase abnormal
Galactose elimination capacity test abnormal	Blood cholinesterase decreased
Galactose elimination capacity test decreased	Deficiency of bile secretion
Gamma-glutamyltransferase abnormal	Glutamate dehydrogenase increased
Gamma-glutamyltransferase increased	Haemorrhagic ascites
Guanase increased	Hepatic fibrosis marker abnormal
Hepaplastin abnormal	Hepatic fibrosis marker increased
Hepaplastin decreased	Hypoalbuminaemia

Table 10. Customised MedDRA Query (CMQ) List of Preferred Terms for Drug Related Hepatic Disorders

Hepatic artery flow decreased	Leucine aminopeptidase increased
Hepatic congestion	Liver function test decreased
Hepatic enzyme abnormal	Liver function test increased
Hepatic enzyme decreased	Liver iron concentration abnormal
Hepatic enzyme increased	Liver iron concentration increased
Hepatic function abnormal	Model for end stage liver disease score abnormal
Hepatic hydrothorax	Model for end stage liver disease score increased
Hepatic hypertrophy	Periportal oedema
Hepatic mass	Peritoneal fluid protein abnormal
Hepatic pain	Peritoneal fluid protein decreased
Hepatic sequestration	Peritoneal fluid protein increased
Hepatic vascular resistance increased	Pneumobilia
Hepatobiliary scan abnormal	Portal vein flow decreased
Hepatomegaly	Portal vein pressure increased
Hepatosplenomegaly	Retinol binding protein decreased
Hyperammonaemia	Urobilinogen urine decreased
Hyperbilirubinaemia	Urobilinogen urine increased
Hepatic disorders specifically reported as alcohol-related	
Alcoholic liver disease	Hepatic steato-fibrosis
Cirrhosis alcoholic	Hepatitis alcoholic
Fatty liver alcoholic	Zieve syndrome

6.7.2 Customised MedDRA Query (CMQ) List of Preferred Terms for Injection Site Reaction

Table 11. Customised MedDRA Query (CMQ) List of Preferred Terms for Injection Site Reaction

Immediate post-injection reaction	Injection site ulcer
Injection related reaction	Injection site urticaria
Injection site abscess	Injection site vesicles
Injection site cellulitis	Injection site warmth
Injection site infection	Injection site ischaemia
Injection site pustule	Injection site coldness
Injection site abscess sterile	Injection site discolouration
Injection site anaesthesia	Injection site photosensitivity reaction
Injection site atrophy	Injection site swelling
Injection site bruising	Injection site discomfort
Injection site cyst	Injection site calcification
Injection site dermatitis	Injection site movement impairment
Injection site erosion	Injection site lymphadenopathy
Injection site erythema	Injection site nodule
Injection site extravasation	Embolia cutis medicamentosa
Injection site fibrosis	Injection site scar
Injection site granuloma	Injection site discharge

Table 11. Customised MedDRA Query (CMQ) List of Preferred Terms for Injection Site Reaction

Injection site haematoma	Injection site pallor
Injection site haemorrhage	Injection site papule
Injection site hypersensitivity	Injection site injury
Injection site hypertrophy	Injection site scab
Injection site induration	Injection site eczema
Injection site inflammation	Injection site streaking
Injection site irritation	Injection site dryness
Injection site mass	Injection site laceration
Injection site necrosis	Injection site macule
Injection site nerve damage	Injection site vasculitis
Injection site oedema	Injection site exfoliation
Injection site pain	Injection site dysaesthesia
Injection site paraesthesia	Injection site plaque
Injection site phlebitis	Injection site hyperaesthesia
Injection site pruritus	Injection site hypoaesthesia
Injection site rash	Injection site hypertrichosis
Injection site reaction	
Injection site thrombosis	

6.8 Appendix 8: Derivation of Overall UDS Result for Opioids Use

Results of on-site dipstick UDS and centrally tested UDS will be used for primary, secondary, [redacted] efficacy endpoints analyses in this SAP. A urine dipstick is performed onsite at Screening, Induction Day 1, and Week 6. UDS samples for all other scheduled visits are tested centrally. In the case that a central UDS sample was not submitted for a scheduled visit, the on-site dipstick UDS, if available for that visit, will be used.

6.8.1 Centrally Tested UDS

Centrally tested UDS provides individual results (negative or positive) for each of the different opioid drugs being tested. To derive the centrally tested overall opioids UDS result, the UDS fentanyl test result will be derived first. Then, results from 3 tests (opiates, fentanyl, methadone) will be used.

The centrally tested UDS fentanyl test result will be based on “Fentanyl” and “Norfentanyl” test results. The algorithm to determine the central UDS fentanyl result is as follows:

- “Fentanyl Positive” if either of the 2 test results is positive.
- “Fentanyl Negative” if both test results are negative; or if 1 is negative and the other is missing.
- “Fentanyl Missing” if both test results are missing.

The algorithm to determine the centrally tested overall UDS opioid result for each visit uses the 3 individual results (fentanyl, opiates, methadone) as follows:

- "Opioid Positive" if at least 1 individual test result is positive.
- "Opioid Negative" if all 3 individual test results are negative.
- "Opioid Missing" for other scenarios, eg, if all 3 individual test results are missing, or if one test result is missing and the other 2 individual test results are either negative or missing.

6.8.2 On-site dipstick UDS

Individual test results for opioids and morphine from the on-site dipstick UDS will be combined into 1 result for opioids/morphine. The algorithm to determine the combined result is as follows:

- "Opioids/morphine Positive" if at least 1 of the individual test results is positive.
- "Opioids/morphine Negative" if both test results are negative; or if 1 is negative and another is missing.
- "Opioids/morphine Missing" if both test results are missing.

The algorithm to determine the on-site dipstick overall UDS opioid result uses 4 test results (1 combined test result for opioids/morphine, and 3 individual test results for oxycodone, methadone, fentanyl) as follows:

- "Opioid Positive" if at least 1 test result is positive.
- "Opioid Negative" if all 4 test results are negative.
- "Opioid Missing" for other scenarios, eg, if all 4 test results are missing; if opioids/morphine is missing and the other 3 test results are negative or missing; if the fentanyl test result is missing and at least one of the other 3 test results is negative.

7 REFERENCES

Song C, Kuznetsova OM. Implementing constrained or balanced across the centers randomization with SAS v8 Procedure PLAN. PharmaSUG 2003 proceedings 2003:473-479.