STATISTICAL ANALYSIS PLAN

for INDV-6000-401 Main 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.

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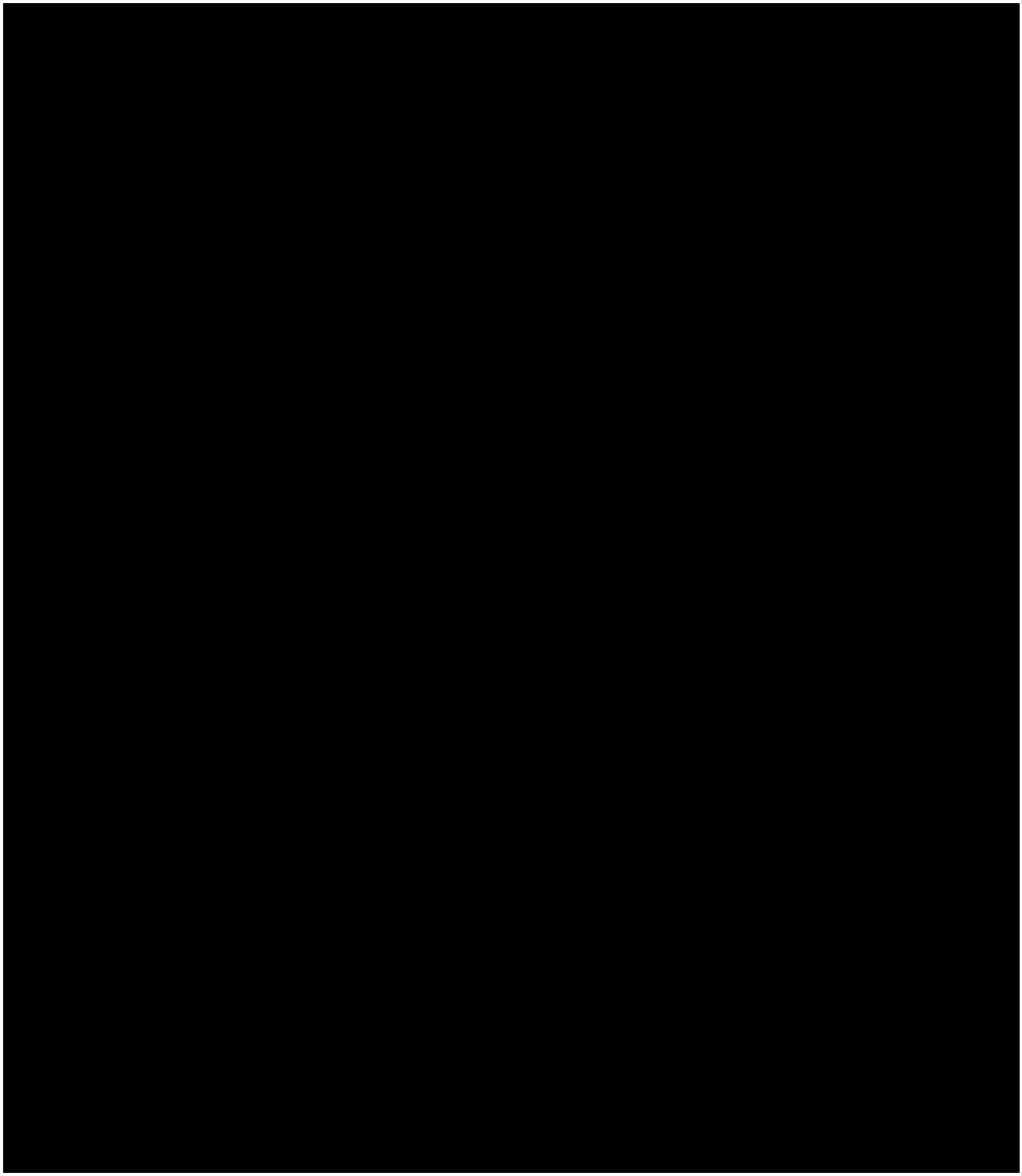
Regulatory Agency Identifier Number(s)

Registry	ID
ClinicalTrials.gov	NCT04995029

Version 1.0: 22 Aug 2024

Statistical Analysis Plan Approval



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1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analysis to be included in the clinical study report for the INDV-6000-401 main study protocol amendment 3 (07APR2022). It is intended to summarize detailed methodology for efficacy, safety, tolerability, and health outcomes analyses. Pharmacokinetic analysis will be presented in a separate PK Analysis Plan and Report. The Open-Label Induction Sub-study analysis is addressed in a separate analysis plan. Tables, listings, and Figures associated with this analysis plan are presented in a separate document.

The preparation of this SAP has been based on International Council for Harmonisation (ICH) E3 and E9 Guidelines.

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	22 Aug 2024	Not Applicable	Original version

1.2 Summary of Key Protocol Information

The pivotal Phase 3 double-blind efficacy study demonstrated that RBP-6000 given as 2 doses of 300-mg followed by 4 doses of 300-mg or 100-mg at 4-week intervals (the 300/300-mg and 300/100-mg dosing regimens, respectively) led to significantly higher percentage abstinence from opioids in participants with moderate or severe opioid use disorder (OUD) compared with placebo. An additional post-hoc observation from this study was that the subgroup of injecting opioid users achieved higher percentage abstinence at Week 24 with the 300/300-mg regimen compared with the 300/100-mg regimen (54% vs 32%, respectively; relative risk=1.7, 95% confidence interval 1.2-2.4). The percentage of injecting opioid users who remained abstinent for the last 4 weeks of the 24-week treatment period, when differences in buprenorphine (BUP) plasma concentrations between the 2 dosing regimens were the greatest, was higher with the 300/300-mg group than with the 300/100-mg group (34% vs 18%). These observations are consistent with the scientific literature indicating that some individuals require higher BUP exposure and higher levels of mu-opioid receptor occupancy to maximise abstinence and retention in treatment (Hillhouse 2011, Romero-Gonzalez 2017).

This 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 OUD and high-risk opioid use (ie those who use opioids via an injection route, for an average of 5 or more days per week and/or use high doses of opioids) that may benefit from the higher 300-mg maintenance dose.

1.3 Study Design

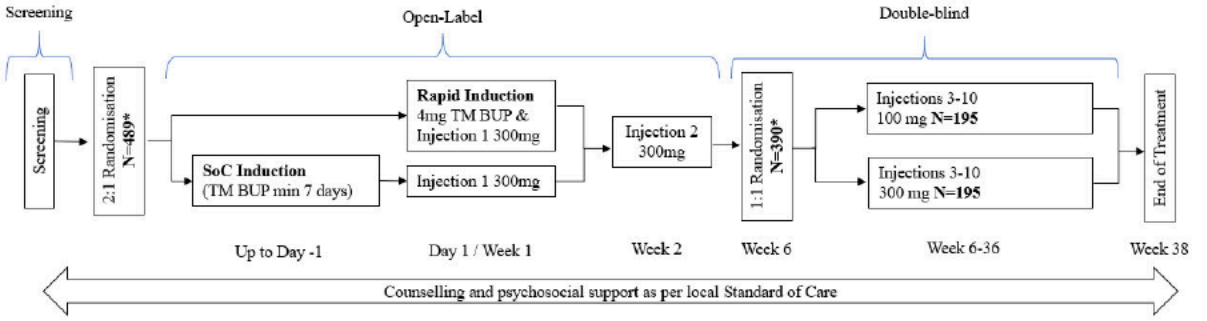
An Open-label Induction Sub-study (OLIS) is nested within this study and will compare treatment retention and safety and tolerability of RBP-6000 in participants following rapid induction or SoC induction. (See Figure 1.) When the participant has met the TM BUP dosing criteria, he/she will be randomised at a 2:1 ratio to RBP-6000 rapid induction or SoC induction. Due to the potential for fentanyl use to impact the response to TM BUP induction, randomisation will be stratified according to the same-day UDS result for fentanyl (negative or positive). The rapid induction arm is designed to initiate RBP-6000 treatment following a single dose of TM BUP, while the SoC induction arm inducts the participant onto RBP-6000 using a TM BUP containing product for a minimum of 7 days. Following TM BUP induction using either rapid induction or SoC induction, and confirmation that the participant is eligible for dosing with RBP-6000, pre–RBP-6000 assessments will be conducted; if eligible, 300-mg RBP-6000 may be administered SC and the visit will be considered Week 1 Day 1. The second RBP-6000 dose will be administered at Week 2, 1 week (+4 days) after the first injection.

Participants eligible to continue treatment will be randomised at Week 6 prior to Injection 3 in a 1:1 ratio to receive double-blind (DB) maintenance doses of either 300-mg or 100-mg every 4 weeks (-2/+4 days) for a total of up to 8 maintenance injections. The DB Randomisation prior to the third RBP-6000 dose will be stratified according to frequent injection route at Screening (inclusion criteria 5a yes or no) and Week 6 UDS result for opioids (negative or positive).

The DB Randomisation was implemented using an Interactive Web Response System (IWRS). The randomisation number, assigned via the IWRS, used central, blocked, stratified randomisation schedules. The randomisation schedules were generated using a balanced-across-centres approach (Song, 2003), with block size of 4 in a 1:1 ratio. Four distinct blocks (CDCD, CDDC, DCDC, DCCD) formed a balanced set for Latin Squares, then the block order was randomly permuted to form a sequence of Latin Squares. A block was dynamically allocated to a site by IWRS, at the time of randomising the first participant at that site. This approach helps balance the treatment assignments across sites when blocks are left incomplete. Note, blocks CCDD and DDCC were excluded to reduce the probability of imbalance within a site.

Participants will return to the site for weekly UDS and collection of self-reported drug use, including TLFB, from Weeks 1 to 10. From the fourth injection until the end of the treatment period (Weeks 10 to 38), UDS and self-reported drug use, including TLFB, will be obtained at every injection visit. In addition, random visits to assess UDS and TLFB (only) will be scheduled by the Investigator in between every injection (2 weeks post each injection ±7 days) from Injection 4 through Injection 10. All participants will receive counselling, per SoC, from Day 1, Week 1, through the end of the treatment period. All participants will continue study treatment until they complete the end-of-treatment (EOT) Visit (Week 38). Participants who prematurely discontinue RBP-6000 treatment will complete the early termination (ET) visit. During the last injection visit (Week 34) through the EOT visit (or the ET for those who prematurely discontinue), the Investigator or a medically qualified sub-Investigator will discuss available options for continued treatment. Any participant with ongoing adverse events (AE) at the EOT or ET visit will also be followed up by phone 2 weeks later for the End of Study (EOS) visit to assess any ongoing AEs and concomitant medications associated with those ongoing AEs only.

Figure 1. Study Schematic



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

1.4 Objectives and Endpoints

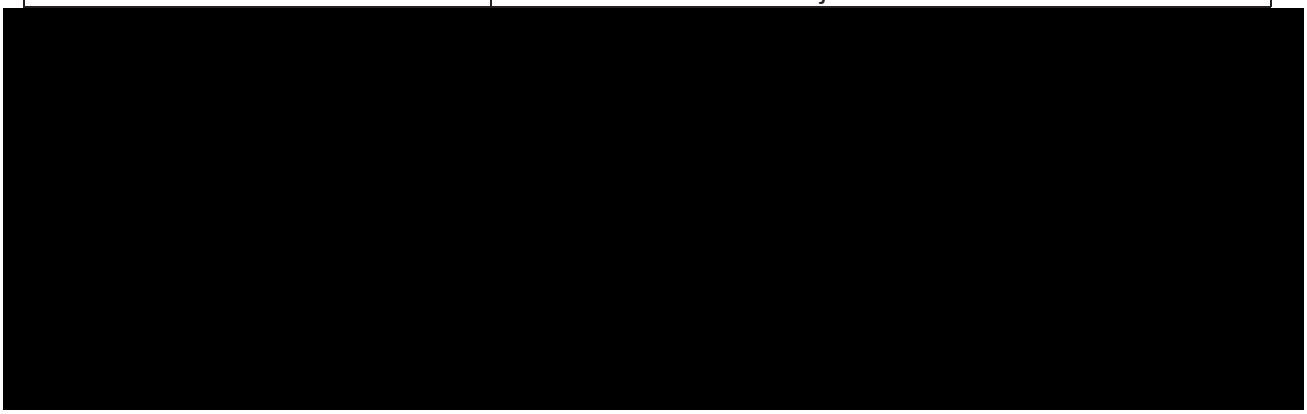
1.4.1 Study Objectives and Endpoints

See Section 6.8 for a Summary of Efficacy Endpoints.

Table 2. Objectives & Endpoints

Objectives	Endpoints
Primary Objective	**Primary Efficacy Endpoint**
Compare the efficacy of 100-mg and 300-mg maintenance doses of RBP-6000 administered every 4 weeks in participants who use opioids via an injection route and/or use high doses of opioids	Proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative Urine Drug Screen (UDS) and Timeline Follow Back (TLFB) for the prior week) is greater than or equal to 80% over Weeks 20 to 38 (inclusive)
Secondary Objective	**Secondary Efficacy Endpoints**
Assess the effect of 100-mg and 300-mg maintenance doses of RBP-6000 administered every 4 weeks on treatment retention and parameters of harm reduction (eg, frequency of opioid use) in participants who use opioids via an injection route and/or use high doses of opioids	1) Participants' percentage of days opioids were used out of days assessed (TLFB) over Weeks 10 to 38 (inclusive) 2) Proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 10 to 38 (inclusive) 3) Participants' percentage of visits with opioid abstinence (defined as negative UDS and Time-Line Follow Back [TLFB] for opioid use) over Weeks 10 to 38 (inclusive) 4) Proportion of responders for weekly opioid use, defined as participants' percentage of visits with

Objectives	Endpoints
	opioid abstinence being greater than or equal to 80% for the last 5 visits planned for UDS and TLFB assessment over Week 30 to Week 38 (inclusive) 5) Proportion of responders for daily opioid use, defined as participants' percentage of days opioids were used out of days assessed (TLFB) being ≤ 20% for participants' last 5 visits with observed TLFB post randomisation 6) Participants' percentage of days opioids were used out of days assessed (TLFB) overall (Week 2 to 38 inclusive) 7) Participants' percentage of visits with opioid abstinence (defined as negative UDS and TLFB for opioid use) overall (Week 2 to 38 inclusive) 8) For participants who use opioids via the injection route for an average of 5 or more days per week in the last 4 weeks prior to Screening, participants' percentage of days opioids were used via the injection route out of days assessed (TLFB) overall (Weeks 10 to 38 inclusive) 9) Average number of times opioids were used per week (TLFB) by visit 10) Change in participants' number of times opioids were used per week from Screening or randomisation baseline to each visit 11) Proportion of participants abstinent (defined as negative UDS and TLFB for opioid use) by visit 12) Average number of days opioids were used per week (TLFB) by visit 13) Treatment retention since randomisation 14) Proportion of randomised participants who complete the last scheduled injection of RBP-6000



Objectives	Endpoints
[redacted]	

Safety Objective	Safety Endpoints
Assess the safety and tolerability of RBP-6000 in participants who use opioids via an injection route and/or use high doses of opioids	• Proportion of participants with at least 1 TEAE of the following types at any time during the treatment period: any TEAE, drug-related TEAE, treatment-emergent serious AE (SAE), drug-related treatment-emergent SAE, or TEAE leading to treatment discontinuation • Laboratory results, vital signs and use of concomitant medications

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1.4.2 Estimands

1.4.2.1 Primary Estimand

Table 3. Primary Endpoint Estimand

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	Population	IES	PLS (Analysis)
Primary Efficacy Endpoint	Difference between treatment arms in the proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 20 to 38 (inclusive)	Study population: OUD treatment-seeking patients who use opioids via an injection route and/or use high doses of illicit opioids. Analysis population: FAS	Composite strategy: Visits with missing opioid assessments, i.e., missing both UDS and TLFB due to discontinuation from the study (monotone missing) or due to skipped visit (intermittent missing), will be treated as non-negative and are de-facto "positive" for opioid use (i.e., worst-case outcome) As a sensitivity analysis, multiple imputation will be performed for the CMH analysis to impute missing and skipped visit values based on the participants' other results in addition to other variables in the dataset. Missing data will be assumed to follow a monotone missing pattern for imputation. The composite strategy may be used in other sensitivity analyses as needed.	Cochran-Mantel-Haenszel test stratified for randomisation stratification to provide the unadjusted treatment group comparison. The unadjusted and risk adjusted difference in treatment effects (300-mg vs 100-mg) will be also estimated using nonparametric ANCOVA accounting for randomisation stratification to provide the 95% CI for unadjusted estimation. See SAP Section 5.1.6 for a list of risk factors to be considered as covariates for risk adjusted estimation.

ANCOVA=analysis of covariance; CI=confidence interval; FAS=Full Analysis Set; IES=intercurrent event(s) strategy; OUD = opioid use disorder; PLS=population-level summary; RF=randomisation factors; TLFB=TimeLine Follow Back; UDS=urine drug screen

Randomisation factors include 1) opioid use via injection route for an average of 5 or more days per week in the past 4 weeks at Screening (yes or no) and 2) Week 6 UDS result (negative or positive for opioids).

1.4.2.2 Secondary Estimands

The secondary estimands are presented in Table 4.

Table 4. Secondary Estimands

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	Population	IES	PLS (Analysis)
Secondary Efficacy Endpoint 1	Participants' percentage of days opioids were used out of days assessed (TLFB) over Weeks 10 to 38 (inclusive)	As primary	While-on-treatment strategy: Missing daily TLFB (monotone or intermittent) will not be imputed. For the participant who has an injection of randomised treatment but without any TLFB assessed post-randomisation (typically a rare occurrence), participant's percentage of days opioids were used will be derived based on his/her last observed TLFB prior to the randomisation, i.e., the TLFB for 7-day opioid use at the randomisation visit or the last observed TLFB after the first injection of RBP-6000 if the TLFB is also missing at the randomisation visit.	Wilcoxon rank-sum test stratified for RF to provide the unadjusted treatment group comparison. The unadjusted and risk adjusted difference in treatment effects (300-mg vs 100-mg) will be also estimated using nonparametric ANCOVA accounting for randomisation stratification to provide the 95% CI for unadjusted estimation. See SAP Section 5.1.6 for a list of risk factors to be considered as covariates for risk adjusted estimation.

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	Population	IES	PLS (Analysis)
Secondary Efficacy Endpoint 2	Proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 10 to 38 (inclusive)	As primary	Composite strategy used in the primary endpoint	As primary
Secondary Efficacy Endpoint 3	Percentage of visits with opioid abstinence (defined as negative UDS and TLFB for the prior week) over Weeks 10 to 38 (inclusive)	As primary	While-on-treatment strategy used in secondary endpoint 1	The unadjusted difference in treatment effects (300-mg vs 100-mg) will be also estimated using nonparametric ANCOVA accounting for randomisation stratification to provide the 95% CI for unadjusted estimation.

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	Population	IES	PLS (Analysis)
Secondary Efficacy Endpoint 4	Proportion of responders for weekly opioid use, defined as participants' percentage of visits with opioid abstinence being greater than or equal to 80% (for the last 5 visits planned for UDS and TLFB assessment over Weeks 30 to 38)	As primary	Composite strategy used in the primary endpoint	As primary
Secondary Efficacy Endpoint 5	Proportion of responders for daily opioid use, defined as participants' percentage of days opioids were used out of days assessed (TLFB) being less than or equal to 20% for participants' last 5 visits with observed TLFB post randomisation	As primary	Composite strategy used in the primary endpoint	As primary

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	Population	IES	PLS (Analysis)
Secondary Efficacy Endpoint 6	Participants' percentage of visits with opioid abstinence (defined as negative UDS and TLFB for opioid use) overall (Weeks 2 to 38 inclusive)	As primary	Composite strategy used in the primary endpoint	As secondary 3
Secondary Efficacy Endpoint 7	Participants' percentage of days opioids were used out of days assessed (TLFB) overall (Weeks 2 to 38 inclusive)	As primary	While-on-treatment strategy: Missing data will not be imputed	As secondary 3
Secondary Efficacy Endpoint 8	Participants' percentage of days opioids were used via the injection route out of days assessed (TLFB) overall (Weeks 10 to 38 inclusive)	FAS subgroup of those with injection opioid use (Section 5.1.6)	While-on-treatment strategy: Missing data will not be imputed	As secondary 3
Secondary Efficacy Endpoint 9	Average number of times opioids were used per week (TLFB) by visit	As primary	While-on-treatment strategy: Missing data will not be imputed Hypothetical Strategy:	The average number of times opioids were used per week (TLFB) for each treatment group will be summarised by visit from Screening to Week 38 for overall and within individual randomisation stratum; the difference between treatment groups will be estimated with a 95% CI for each visit.

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	Population	IES	PLS (Analysis)
			Potentially erroneous result entries that are >30 with >50% increase from the next highest entry per participant will be imputed as missing.	
Secondary Efficacy Endpoint 10	Change in participants' number of times opioids were used per week from Screening or randomisation Baseline to each visit	As primary	While-on-treatment strategy: Only the participants with complete 7-daily TLFB information for a given visit will be analysed for that visit. Hypothetical Strategy: The participants with partial daily TLFB information at a given visit will be imputed as the total number of times opioids were used divided by the number of days with observed TLFB information times 7 for that visit.	The mean change value or percentage change value from Screening or DB randomisation Baseline for each treatment group will be summarised by visit from Screening or randomisation Baseline to Week 38 for overall and within individual randomisation stratum; the difference between treatment groups will be estimated with a 95% CI for each visit.
Secondary Efficacy Endpoint 11	Proportion of participants abstinent (defined as negative UDS and TLFB for opioid use) by visit.	As primary	Composite strategy used in the primary endpoint	Proportion of participants abstinent will be estimated with 95% CI by visit for individual treatment groups from Screening to Week 38. The difference between the treatment groups will be estimated with 95% CI by visit.
Secondary Efficacy Endpoint 12	Average number of days opioids were used per week (TLFB) by visit	As primary	While-on-treatment strategy: Missing data will not be imputed.	The average number of days opioids were used per week (TLFB) for each treatment group will be summarised by visit from Screening to Week 38 for overall and within individual randomisation stratum; the difference between treatment groups will be estimated with a 95% CI for each visit.
Secondary Efficacy Endpoint 13	Treatment retention since DB randomisation	As primary	Not applicable: Intercurrent events are not relevant for this endpoint.	Kaplan-Meier method to describe the survival curves

Statistical Category	Estimand Attributes			
	Variable/ Endpoint	Population	IES	PLS (Analysis)
Secondary Efficacy Endpoint 14	Proportion of randomised participants who complete the last scheduled injection of RBP-6000	As primary	Not applicable: Intercurrent events are not relevant for this endpoint.	As primary

ANCOVA=analysis of covariance; CI=confidence interval; FAS=Full Analysis Set; IES=intercurrent event(s) strategy; OUD = opioid use disorder; PLS=population-level summary; RF=randomisation factors; TLFB=TimeLine Follow Back; UDS=urine drug screen

The 2 RFs are: 1) opioid use via injection route for an average of 5 or more days per week in the past 4 weeks at Screening (yes or no) and 2) Week 6 UDS result (negative or positive for opioids).

2 STATISTICAL HYPOTHESES

This study is designed to compare the efficacy of 100-mg and 300-mg maintenance doses of RBP-6000 administered every 4 weeks in participants who use opioids via an injection route and/or use high doses of opioids. Statistical superiority of the 300-mg maintenance dose over the 100-mg maintenance dose will be concluded if the difference between the proportion of responders for weekly opioid use between the 2 arms (300-mg – 100-mg) is >0 and the 2-sided p-value is ≤0.05. A responder is defined as a participant whose percentage of visits with opioid abstinence (as measured via negative UDS and TLFB for the prior week) is greater than or equal to 80% over Weeks 20 to 38.

The null and alternative hypotheses are as follows:

H_0: proportion of responders $_{300mg}$ = proportion of responders $_{100mg}$

H_A: proportion of responders $_{300mg}$ > proportion of responders $_{100mg}$

2.1 Multiplicity Adjustment

There is only one statistical inferential test for the primary endpoint so there is no multiplicity issue associated with the primary endpoint. For the secondary endpoint 1, a gate keeping strategy will be applied, that is, only after the primary endpoint test is statistically significant, the statistical test result for this endpoint will be used inferentially at 5% alpha level. All other statistical tests for the rest of the study, including supplemental, sensitivity and exploratory tests for the primary endpoint and secondary endpoint 1, will be assessed at a nominal 2-sided 5% alpha level without multiplicity adjustments.

3 SAMPLE SIZE DETERMINATION

Post-hoc analyses of the injecting opioid users in the Phase III DB study showed that the proportions of responders (where a responder was defined as a participant having at least 80% of weeks with opioid use abstinence [UDS and TLFB combined] during Week 10 through Week 25 corresponding to assessments post RBP-6000 Injections 3 through 6) were 44.4% and 28.8% for 300-mg and 100-mg maintenance doses, respectively, leading to a responder rate difference (95% CI) of 15.66% (-0.77%, 32.08%).

For the primary efficacy endpoint (proportion of responders for weekly opioid use over Weeks 20 to 38), a sample size of 195 per group will provide approximately 90% power at 2-sided 0.05 alpha level to detect a difference of 15.6%.

Since the study population in this study has more severe OUD compared with the Phase III DB study, the responder rates and treatment differences may be lower. To evaluate this possibility, the responder rates required for the RBP-6000 300-mg group to achieve at least 80% power with N=195 per group under various assumptions for responder rates in the RBP-6000 100-mg group are summarised in Table 5. In addition, the power under various assumptions for the RBP-6000 100-mg and 300-mg groups and using 2-sided 0.05 alpha level with N=195 per group is summarized in Table 6.

Table 5. RBP6000 300-mg Responder Rate for the Binary Primary Endpoint Comparison Required Under Assumptions of a Lower RBP6000 100-mg Responder Rate

RBP-6000 100-mg Responder Rate	Required RBP6000 300-mg Responder Rate to Achieve at least 80% Power
5%	13.2%
10%	20.2%
15%	26.5%
20%	32.5%
25%	38.2%
28.8%	42.3%

Note: The required RBP-6000 300-mg responder rate is calculated to achieve at least 80% power with 2-sided alpha=0.05 and 195 participants per group.

Table 6 Power Under Various Assumed Responder Rates for RBP-6000 300-mg and RBP-6000-100-mg

	RBP-6000 300-mg Responder Rate						
RBP-6000 100-mg Responder Rate	**10%**	**15%**	**20%**	**25%**	**30%**	**35%**	**40%**
5%	47%	91%	99%				

10%		32%	79%	98%	99%		
15%			25%	70%	95%	99%	
20%				22%	63%	92%	99%
25%					20%	58%	89%
30%						18%	54%

Note: Power calculations using 2-sided alpha=0.05 and 195 participants per group.

Randomisation will occur and the maintenance doses will begin for eligible participants following completion of the OLTP of the study. A minimal dropout rate of 20% is anticipated to occur during the OLTP, prior to randomisation (see study schematic in Section 1.3). Therefore, the number of participants entering the OLTP will be increased accordingly, to ensure there are enough participants remaining to randomise N=390 participants following the OLTP.

4 POPULATIONS FOR ANALYSIS

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

The analysis populations are defined as shown in Table 7.

Table 7. Population for Analysis

Population	Description
Screened	Participants who signed the informed consent form.
Double-blind (DB) Randomised	Participants who were randomised to the RBP-6000 maintenance dosage groups at Week 6 (Injection 3). Participants will be analysed according to the randomised treatment group.
Full Analysis Set (FAS)	Participants who met all inclusion/exclusion criteria, were randomised, and received at least 1 maintenance RBP-6000 injection post-DB Randomisation. Participants will be analysed according to the randomised treatment group. This population will serve as the primary analysis population for efficacy analysis.
Double-Blind (DB) Safety	Participants who received at least 1 maintenance RBP-6000 injection post DB Randomisation. This population would be the same as the FAS except the participants will be analysed corresponding to the maintenance dosage they actually received. Any participant who receives incorrect study treatment for the entire Double-blind Treatment Period (DBTP) will be included in the treatment group corresponding to the study treatment received. This population will serve as the population for all DB safety analyses.
Open-Label (OL) Safety	Participants who received at least 1 post-enrolment open-label RBP-6000 injection.

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5 STATISTICAL ANALYSES

5.1 General Considerations

The SAP is prepared after the protocol is approved and will be signed off before database lock occurs. The SAP provides further details regarding analyses outlined in the protocol. Additional unplanned analyses may be required after all planned analyses have been completed. Any unplanned analyses or deviations from the analyses described below will be outlined in the Clinical Study Report (CSR).

Continuous variables will be summarised using descriptive statistics such as mean, standard deviation [SD], median, quartiles, minimum, and maximum. Categorical variables will be reported as frequency counts (including number missing) and the percentage of participants in corresponding categories. All categories will be presented, even if no participants are counted in a particular category.

Individual participant data will be presented by participant in data listings for either the Screened Population or OL Safety Population unless otherwise specified. Data listings will include all data collected from the initial Screening Visit to Week 38/EOT Visit, including unscheduled and ET visits. Population indicators for the OL Safety, DB Safety, or FAS populations will be presented as needed. Data listings in safety analysis will be presented for OLTP and DBTP separately.

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 each analysis description.

All tables, statistical analyses, figures, and participant data listings will be generated using SAS® Version 9.4 or SAS EG Version 7.1 (SAS Institute Inc., Cary, North Carolina, United States) on a Unix operating system.

5.1.1 Definition of Baseline

For all assessments, the Baseline value will be considered the latest value prior to the applicable timepoint as illustrated in Table 8. If no pre-dose value exists, the value on the date of the dose will be taken.

Table 8. Baseline Definitions

Baseline Type	Definition
Screening Baseline	The value collected during the Screening period. The Screening visit result should be prioritized. If a Screening visit result is not available, then the most recent value prior to the first dose of TM-BUP should be used.
Pre–Open-label Injection Baseline	The most recent value available prior to the Week 1 Day 1 RBP-6000 injection
Pre-Double-blind (DB) Injection Baseline	The most recent value available prior to the Week 6 RBP-6000 injection

Unless otherwise stated, if Baseline data are missing, no derivation will be performed and Baseline will be set to missing. The change from Baseline will be calculated as follows:

Change = (post-Baseline value – Baseline value).

5.1.2 Visit Mapping

All data included in table outcomes will be analysed according to the nominal visit and time at which it was collected. Unscheduled assessments covering missed or skipped visits will not be considered, however, missed visit results may be imputed depending on the planned analysis. If multiple records exist prior to the Week 1 Day 1 dose, the entry with the most recent administration date that falls on the date of first injection should be assigned as the Week 1 Day 1 result.

Unscheduled visit results will be considered for use in figures and will be listed.

5.1.3 Study Periods

Study periods will be defined as below in Table 9. The schedules of events may be referenced in 6.3the protocol. Data presented in the Open-label Induction Substudy CSR will not be included in this analysis unless otherwise specified (eg, Safety summaries).

Table 9. Study Period Definitions

Study Period	Date Range (Start and End Date)
Screening	Start: Screening visit date (or rescreened date, if applicable) End: Prior to the first dose of Induction treatment, TM BUP

Induction Period	Start: The date/time for the first dose of induction treatment, TM BUP End: Prior to the first RBP-6000 injection on Day 1
Open-label Treatment Period (OLTP)	Start: The date/time of the first RBP-6000 injection End: Prior to the date/time of RBP-6000 Injection 3 scheduled at the Week 6 Visit
Double-blind Treatment Period (DBTP)	Start: the date/time of the scheduled Week 6 RBP-6000 Injection 3 or the date/time of DB Randomisation if Week 6 RBP-6000 Injection 3 was not administered End: The Week 38 or Early Termination (ET) Visit date
Overall RBP-6000 Treatment Period	Start: The date/time of the first RBP-6000 injection End: The Week 38 or Early Termination (ET) Visit date

The study day for each period will be calculated as below as necessary. Study day = Assessment date – start date of study period + 1, if date of assessment is on or after the start date of study period

or

Study day = Assessment date – start date of study period, if date of assessment is prior to the start date of study period

5.1.4 Study Treatment Groups

Treatment groups will be summarized as follows in Table 10.

Table 10. Treatment Group Descriptions

Double-Blind Summaries		
Group	**Definition**	**Order in TLF**
300-mg	RBP-6000 maintenance 300-mg dosage	1
100-mg	RBP-6000 maintenance 100-mg dosage	2
Total	All population participants	3
Screening & Open-Label Safety Summaries		
Group	**Definition**	**Order in TLF**
Screened	All participants screened who did not receive an induction dose of TM BUP (Screened Population only) *	1
Induction	All participants who received an induction dose of TM BUP but did not receive an initial dose of RBP-6000 (Screened Population only) *	2
OL RBP-6000	All who received an RBP-6000 initial dose but did not receive a maintenance dose (Injection 3)	3
DB RBP-6000	All who received an RBP-6000 maintenance dose	4
Total	All population participants	5

*Only used in Screened Population summaries

Participants may be analysed corresponding to the treatment group to which they were randomised ("as randomised") or corresponding to the treatment group to which they received ("as treated"), as stated in the analysis populations definitions (Section 4) or in the analysis sections for each endpoint. If a DB randomised participant is re-randomised due to operation error, the initial DB Randomisation will be used.

5.1.5 Randomisation Stratification Variables

The DB Randomisation will be stratified according to 1) whether the participant uses the injection route (yes/no) and 2) their Week 6 UDS result for opioids (negative/positive). The 4 randomisation strata for DB Randomisation are as follows:

Strata		
Injection Route	**Opioid UDS (Week 6)**	**Strata Number**
Yes	Positive	1
	Negative	2
No	Positive	3
	Negative	4

The injection route use stratum is defined as meeting protocol Inclusion Criterion 5a: Opioid use via injection route for an average of 5 or more days per week in the past 4 weeks at Screening.

A urine dipstick performed on site at Week 6 is used to provide individual results (negative or positive) for each of the different drugs being tested. Among those, results from 4 UDS tests (opioids/morphine, oxycodone, methadone, and fentanyl) are used to derive the opioid use for randomisation stratification. The algorithm to determine the opioids stratum based on Week 6 UDS result was as follows:

- "Opioid Positive" is determined if at least 1 nonmissing individual result among the 4 tests is positive.
- "Opioid Negative" is determined if all test results are negative.

There is a possibility that the incorrect stratum was used for DB Randomisation due to a data entry error. In all cases, the stratum for randomisation in IWRS will be used in the analysis, if not otherwise specified.

Randomisation strata may be included as modelling covariates, as necessary.

5.1.6 Covariates & Subgroups

The following risk factor variables will be considered as model covariates for applicable analyses.

Table 11. Risk Factor Covariates

Risk Factor/Covariate	Type	Definition and Derivation
Age	Continuous (in years)	
Age Group	Categorical	≥18 to <30, ≥30 to <45, ≥45 to <60, ≥60 to ≤65, >65
Gender	Binary	Sex at birth: male vs female
Race	Binary	Black/African American vs non-Black/African American *May also be used as a subgroup
BMI	Continuous (kg/m^2)	
BMI Group	Categorical	<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, ≥40
Lifetime opioid use	Continuous (in years)	Calculated as Screening Visit date – opioid use start date (year only if necessary) +1.
Baseline Nicotine use	Binary (Yes/No)	Yes (Current), No (Former, Never)
Baseline Alcohol use	Binary (Yes/No)	Yes (Current), No (Former, Never)
Percentage of opioids abstinence during Open-label injections	Continuous (%)	Number of negative opioid use divided by the number of assessments (UDS and self-reported TLFB combined) in the OLTP (Weeks 2 to 6).
Baseline Fentanyl use	Binary (Yes/No)	Fentanyl use will be defined as participants with self-reported fentanyl use in the past 4 weeks (Drug use history) prior to Screening, or with either self-reported TLFB or UDS-detected fentanyl use (during OL dosing) before the first DB RBP-6000 maintenance dose injection.
Baseline Cocaine use	Binary (Yes/No)	Cocaine use will be defined as participants with ongoing cocaine use (Drug use history) or with self-reported TLFB or UDS-detected cocaine use (during OL dosing) before the first DB RBP-6000 maintenance dose injection.
Baseline Marijuana /cannabinoid use	Binary (Yes/No)	Same derivation strategy as Cocaine use.
Baseline Amphetamines /methamphetamine use	Binary (Yes/No)	Same derivation strategy as Cocaine use.
[redacted]		
Pre-existing psychiatric disorder	Binary (Yes/No)	"Yes" where the capitalized medical history term includes any of the following: "DEPRESS", "ANXIETY", "BIPOLAR", "SCHIZOPHREN"

		Otherwise "No"
OUD Severity	Binary (Moderate/Severe)	"Severe" where the medical history term (MHTERM) contains the word 'Severe' "Moderate" where the medical history term (MHTERM) contains the word 'Moderate'
Prior detox from opioids	Binary (Yes/No)	Screening Visit Medication for Opioid Use Disorder form
Overdose History	Binary (Yes/No)	As reported in the CRF question "Has participant ever had an opioid overdose that required assistance from others, an ED visit, or hospitalization?"

The following subgroups or subpopulations may be considered for applicable analyses. When sample size is too sparse, subgroup analyses may not be performed.

Table 12. Subgroups / Subpopulations

Subgroup	Type	Definition and Derivation
Completers	Binary (Yes/No)	"Yes" for all FAS participants who complete the Week 38 End of Treatment visit. Otherwise "No"
Injection Compliant	Binary (Yes/No)	"Yes" for FAS participants who meet the following criteria: 1) Received all administered injections inside of an appropriate exposure window. Participants meeting the following criteria will be excluded: a) Participants with at least 1 injection interval <26 days (based on the label for SUBLOCADE dosing, which says a minimum of 26 days between dosing) b) Participants with at least 1 injection interval >42 days (based on the label for SUBLOCADE dosing, which says an occasional delay is acceptable) c) Participants with ≥2 consecutive injection intervals >36 and ≤42 days (to address more frequent delays) Treatment discontinuation status will not be considered. Participants who took additional concomitant BUP will not be excluded Otherwise "No"

Subgroup	Type	Definition and Derivation
Injecting Opioid Participants	Binary (Yes/No)	"Yes" for FAS participants who meet 1 of the following criteria: 1) Inclusion Criterion 5a met (using opioids via the injection route for an average of 5 or more days per week in the last 4 weeks) 2) Reporting injection as the main route of opioid use in the past 4 weeks prior to screening (Drug use history) Otherwise "No"
High-dose Opioid Use	Binary (Yes/No)	"Yes" for FAS participants who meet Inclusion Criterion 5b (using at least 500 mg IV heroin equivalent [e.g., 1250 mg IV morphine] or self-reported use of any dose of highly potent synthetic opioids [fentanyl and analogues excluding transdermal patches] for an average of 5 or more days per week in the last 4 weeks by any route). Otherwise "No"
Fentanyl Use	Binary (Yes/No)	"Yes" for participants with self-reported fentanyl use in the past 4 weeks (drug use history) prior to Screening or with self-reported or UDS-detected fentanyl use, including nor-fentanyl, during OL sub-study before the first DB RBP-6000 maintenance dose injection. Otherwise "No"
Non-Fentanyl Opioid Use	Binary (Yes/No)	"Yes" for participants who did **NOT have (1)** self-report fentanyl use in the past 4 weeks (drug use history) prior to Screening and **(2)** self-reported or UDS-detected fentanyl or nor-fentanyl use (during OL sub-study) before the first DB RBP-6000 maintenance dose injection. Otherwise "No"
Multiple (substance) vs Opioid Alone Use	Binary (Multiple/Opioids Only)	"Multiple" for participants with self-reported non-opioid use in the past 4 weeks (drug use history) prior to Screening or with self-reported or UDS-detected non-opioid use (during OL sub-study) before the first DB RBP-6000 maintenance dose injection. "Opioids Alone" for participants with **NO** self-reported non-opioid use in the past 4 weeks (drug use history) prior to Screening and **NO** self-reported or UDS-detected non-opioid use (during OL sub-study) before the first DB RBP-6000 maintenance dose injection.

5.2 Study Population Analysis

5.2.1 Participant Demographics

The following demographics and Baseline characteristics will be summarised for the FAS population by DB randomised treatment group using descriptive statistics:

- Sex
- Race, Ethnicity
- Age, Age group (≥18 to <30, ≥30 to <45, ≥45 to <60, ≥60 to ≤65, >65)
- Screening Height, Weight, BMI, BMI Group (<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, ≥40)
- Nicotine use
- Alcohol use
- Caffeine use
- Psychiatric history (Section 5.1.6 overall and by category: Depression, Anxiety, Bipolar, Schizophrenia)
- Drug use history*
    - Non-opioids list: Cocaine, Marijuana/Cannabinoids, Barbiturates, Benzodiazepines, Amphetamines, Methamphetamine, Phencyclidine
    - Opioids list: Heroin, Fentanyl, Hydrocodone, Oxycodone, Morphine, Buprenorphine, Methadone, Other
- Lifetime opioid use (Section 5.1.6)
- Severity of OUD (Moderate, Severe)
- Route of opioid use (Injection, Smoking, Oral, Snorting, Other)
- Status of multiple drug use vs Opioid use alone (Multiple, Opioids alone)
- Baseline Combination Fentanyl + Other Drug Use: % with Baseline UDS positive for Fentanyl plus each other non-opioid UDS substance independently (eg, Fent + Cocaine, Fent + Cannabinoids, etc.)
- Overdose history (including whether the event occurred >1 time)
- Prior use of medication for OUD
- Open-label Opioid Abstinence Percentage (Section 5.1.6)

[redacted]

[redacted]

*All drugs listed in drug use history will be considered present if either checked on the drug use history eCRF page or if the pre–DB Randomisation TLFB or UDS show positive for the opioid being considered as mentioned in Section 5.1.6.

Overall Medical History will also be summarized. The number and percentage of participants reporting medical history events will be tabulated by SOC and PT, by decreasing frequency, for the FAS using descriptive statistics and observed data. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Qualitative variables (e.g., sex, race) will be summarised using frequencies; quantitative variables (e.g., age, weight, height) will be summarised (e.g., using mean, SD, median, 1st quartile, 3rd quartile, minimum, and maximum).

5.2.2 Participant Disposition

Summaries of participant enrolment and disposition will be presented by DB randomised treatment group and overall. A summary of all populations will be presented for the Screened population. Specifically, enrolment will be summarized by the number and percentage of participants belonging to the following categories:

- Screened Population: Participants screened.
- Induction Treated: Participants receiving at least 1 dose of TM BUP in the Induction Period.
- Open-label Safety Population: Participants receiving at least 1 dose of RBP-6000 in the Open-label Safety Period.
- Double-blind Randomised Population: Participants randomised to the DBTP.
- FAS Population: Participants who met all inclusion/exclusion criteria with at least 1 RBP-6000 maintenance dose in the DBTP as presented by their randomised dose.
- Double-Blind Safety Population: Participants with at least 1 RBP-6000 maintenance dose in the DBTP as presented by their actual dose.

Disposition will be summarized for the DB Randomised and the FAS Populations by the number and percentage of participants belonging to the following categories:

- Participants who completed the DBTP at Week 38
- Participants who prematurely discontinued from the DBTP and the reasons for discontinuation

If a participant electively refrains from dosing at a scheduled injection visit without formally discontinuing treatment, they will still be considered on treatment and on study. If the participant has permanently discontinued study treatment and is no longer being followed for

study assessments and procedures (including follow-up procedures), he/she will be considered to have prematurely discontinued treatment.

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

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

Participants who were randomised using the incorrect DB randomisation stratum (i.e., the stratum used in the IWRS for randomisation stratification does not match the stratum data as collected on the eCRF), will be listed with their randomisation information and eCRF stratum data. Participants re-randomised in error will also be listed along with any recorded dosing that does not match the original randomisation.

Information on screening, enrolment, randomisation, analysis populations, study completion, and discontinuation will also be displayed in participant listings.

5.2.3 Protocol Deviations

The number and percentage of participants with important (key) protocol deviations will be summarised by DB treatment, site, and overall for the FAS Population.

5.3 Efficacy Analyses

As a general convention in all efficacy analyses, when percentages or proportions are 0% or 100%, the Clopper-Pearson formula will be used to calculate confidence intervals. See Section 6.8 for a Summary of Efficacy Endpoints.

5.3.1 Primary Efficacy Endpoint

5.3.1.1 Definition of Endpoint

The primary objective will be evaluated for the FAS by comparing the RBP6000 300-mg and 100-mg maintenance dosage groups on the primary endpoint: proportion of responders for weekly opioid use, where a responder is defined as a participant whose percentage of visits with opioid abstinence (defined as negative UDS and TLFB for opioid use) is ≥ 80% over Weeks 20 to 38 (inclusive, based on 10 assessments: 6 scheduled UDS and TLFB assessments and 4 planned random UDS and TLFB assessments).

5.3.1.1.1 Opioid Use Derivation

The percentage of visits with opioid abstinence for an individual participant will be derived as their number of visits with negative assessments divided by 10 (the number of the planned visits for opioid use assessments over Weeks 20 to 38). Under this derivation, any missed or skipped visits will not be counted towards the percent of abstinent visits and will, therefore, be counted as non-negative, or de-facto positive, in accordance with the composite intercurrent event strategy (IES). The 6 scheduled assessments are at Weeks 22, 26, 30, 34, 36, and 38. The

4 planned random assessments are at Weeks 20, 24, 28, and 32. A participant with 8 or more opioid-negative visits over Weeks 20 to 38 (i.e., greater than or equal to 80%) will be classified as a responder, otherwise as a nonresponder.

Overall opioid use based on the 7-daily TLFB for the prior week at a visit will be derived according to Table 13, and opioid use at a visit combining UDS and overall TLFB opioid use will be derived according to Table 14.

Table 13. Overall TLFB Opioid Use Derivation Based on Daily TLFB Results at a Given Visit

	Daily TLFB Opioids		
	All Days=Missing	**All Nonmissing Days=Did Not Use**	**Any Day=Used**
Overall TLFB Opioids	Missing	Negative	Positive

TLFB=TimeLine Follow Back

Table 14. Opioid Use Assessment Combining UDS and Overall TLFB Results at a Given Visit

		Overall TLFB Opioids		
		Missing	**Negative**	**Positive**
UDS Opioids	**Missing**	Missing	Negative	Positive
	Negative	Negative	Negative	Positive
	Positive	Positive	Positive	Positive

TLFB=TimeLine Follow Back; UDS=urine drug screen

Refer to Section 6.4 (appendix) for the derivation of UDS results for overall opioids use. Positive fentanyl UDS will be confirmed/determined by the fentanyl quantification test only, the nor-fentanyl quantification test will not be used. Refer to Section 6.4 (appendix) for the imputation/derivation of opioids use for daily TLFB results. Missing data will be handled in accordance with the Intercurrent Event Strategy (IES) aligned with each endpoint. For the main analytical approach of the primary endpoint, missing data will be considered non-negative, or de-facto positive.

5.3.1.2 Main Analytical Approach

The difference between DB treatment groups will be compared using a Cochran-Mantel-Haenszel (CMH) test accounting for randomisation stratification (Opioid injection use: Yes/No, Week 6 UDS Fentanyl result: Positive/Negative) as described in Section 5.1.6.

The CMH weighted treatment difference and it's 95% CI will be presented. The 95% CI will use the variance estimator presented by Sato (1989) which is shown to be consistent in both sparse and large strata.

The CMH estimate of the treatment difference will be calculated as a weighted average of the strata-specific estimates of the treatment difference calculated within each of the four analysis strata:

1-Injection Route-“YES” and Opioid UDS=”Positive”

2- Injection Route-“YES” and Opioid UDS=”Negative”

3-Injection Route-“NO” and Opioid UDS=”Positive”

4- Injection Route-“NO” and Opioid UDS=”Negative”

If n_k is the number of 300-mg treated participants, m_k is the number of 100-mg treated participants, and $N_k = n_k + m_k$ is the total number of participants in the kth stratum, $\hat{d}_k$ is the estimate of the difference in proportions between the two treatment arms for the kth stratum, then the CMH estimate is given by:

$$\hat{d}_{cmh} = \frac{\sum W_k \hat{d}_k}{\sum W_k}$$

Where W_k is the CMH weight of the kth stratum as:

$$W_k = \frac{n_k m_k}{N_k}$$

The two-sided 95% CI for the CMH difference will be calculated as:

$$\hat{d}_{cmh} \pm 1.96\, x \sqrt{\widehat{var}(\hat{d}_{cmh})}$$

where the variance estimator (Sato, 1989) is given below:

$$\widehat{var}(\hat{d}_{cmh}) = \frac{\hat{d}_{cmh}(\sum P_k) + \sum Q_k}{(\sum n_k m_k / N_k)^2} = \frac{\hat{d}_{cmh}(\sum P_k) + \sum Q_k}{(\sum W_k)^2}$$

where

$$P_k = \frac{n_k^2 y_k - m_k^2 x_k + n_k m_k (m_k - n_k)/2}{N_k^2}$$

$$Q_k = \frac{x_k (m_k - y_k)/N_k + y_k (n_k - x_k)/N_k}{2}$$

where x_k and y_k correspond to the number of responders in the 300-mg and 100-mg treatment groups respectively, for the kth stratum.

Statistical superiority will be concluded if the CMH weighted difference in proportion of responders in the 300-mg maintenance dosage group minus the proportion of responders in the 100-mg maintenance dosage group is >0 and the 2-sided p-value of CMH test ≤0.05.

Descriptive results will include a summary of the proportion of responder outcomes (95% CI) and the difference (95% CI) between DB treatment groups for overall and for individual randomisation strata.

5.3.1.3 Supplemental Analysis

Supplementary analysis will be performed using nonparametric randomisation-based ANCOVA (Koch 1998, Zink 2012). This method uses weighted least-squares to generate covariate-adjusted treatment effects with minimal assumptions. It is general in its applicability to a variety of outcomes, whether continuous, binary, ordinal, incidence density, or time-to-event, and has several advantages including the following: applicability to a variety of outcomes (continuous, binary, etc), minimal assumptions, straightforward to accommodate stratification and greater power of the adjusted treatment effect relative to the unadjusted. Covariance-adjustment in the treatment-effect estimates is a result of the assumed null difference in covariate means which is a consequence of the underlying assumption of randomisation to treatment.

Nonparametric randomisation-based ANCOVA will be performed to account for the randomisation strata and adjust imbalance of risk factor distributions between the 2 randomised arms to obtain the treatment effect difference. This analysis will be performed in 2 ways: firstly, account for randomisation strata but unadjusted for risk factors; secondly, account for randomisation strata and adjusting for all risk factors listed in Section 5.1.6 (age and BMI will be included on a continuous scale only) allowing for risk-adjusted treatment effects to be estimated. The unadjusted and risk adjusted difference of the responder rates between DB treatments and 95% CI and p-value will be estimated.

The %NParCov3 SAS/IML macro (Zink 2012, see example 4.1) will be used to perform the analysis. The binary outcome of the proportion of responders will be input as numeric (0, 1). There should be no transformation used in the model. Weighted estimates of treatment differences should be taken across strata prior to covariance adjustment.

5.3.1.4 Sensitivity Analyses

Sensitivity analyses will be performed for the primary endpoint as follows. Results may be presented in a separate report if necessary.

1) An additional primary endpoint derivation will disregard the UDS fentanyl result, due to uncertain duration of the urine fentanyl test staying positive since the last fentanyl use. The overall UDS result for opioid use will be based on the tests for opiates and methadone only. The CMH weighted treatment group difference, 95% CI, and p-value will be produced.

2) The primary endpoint analysis will be re-derived imputing non-negative, ie positive, results for all participants' post-discontinuation visits (ie monotone missing) if they discontinued due to either lack of efficacy of due to an AE. Post-discontinuation missing visit data from those who discontinue for other reasons will not be imputed and their percentage abstinence will be calculated using a denominator of the number of visits with an opioid assessment. This is intended to assist in limiting the potential bias towards failure for discontinuers. Intermittent missing data will be treated as observed and not imputed. The CMH weighted treatment group difference, 95% CI, and p-value will be produced.

3) Missing data will also be addressed using the multiple imputation technique which creates a random sample of missing values that may plausibly represent the missing data. The multiple samples of data are then analysed using standard procedures and results combined. This is captured by a 3-step approach (Berglund 2014):

   a. Imputation Phase: 50 imputed datasets will be generated to impute missing opioid use outcomes using SAS Proc MI with a monotone logistic regression approach.

      Due to the expectation that missing data will be most prominent after a participant drops from the study, the monotone missing data pattern will be assumed. The monotone pattern is a pattern of missingness, such that if a given visit has a missing value, all subsequent visits most likely to be missing as well. Missing data are assumed to be Missing at Random (MAR) using this approach. The number of imputed datasets may be increased (i.e., >50) if the resulting imputation diagnostics do not converge appropriately.

      Opioid use outcomes ("Negative" or "Positive") will be derived for all participants' non-missing visits as described in Section 5.3.1.1.1. After this is performed, the following variables and covariates will be utilized to impute missing opioid use assessments for each participant: all risk factors listed in Section 5.1.6 (excluding categorical age and BMI), and the observed overall opioid use assessments since DB randomisation. Imputation will be performed separately for participants in each treatment arm.

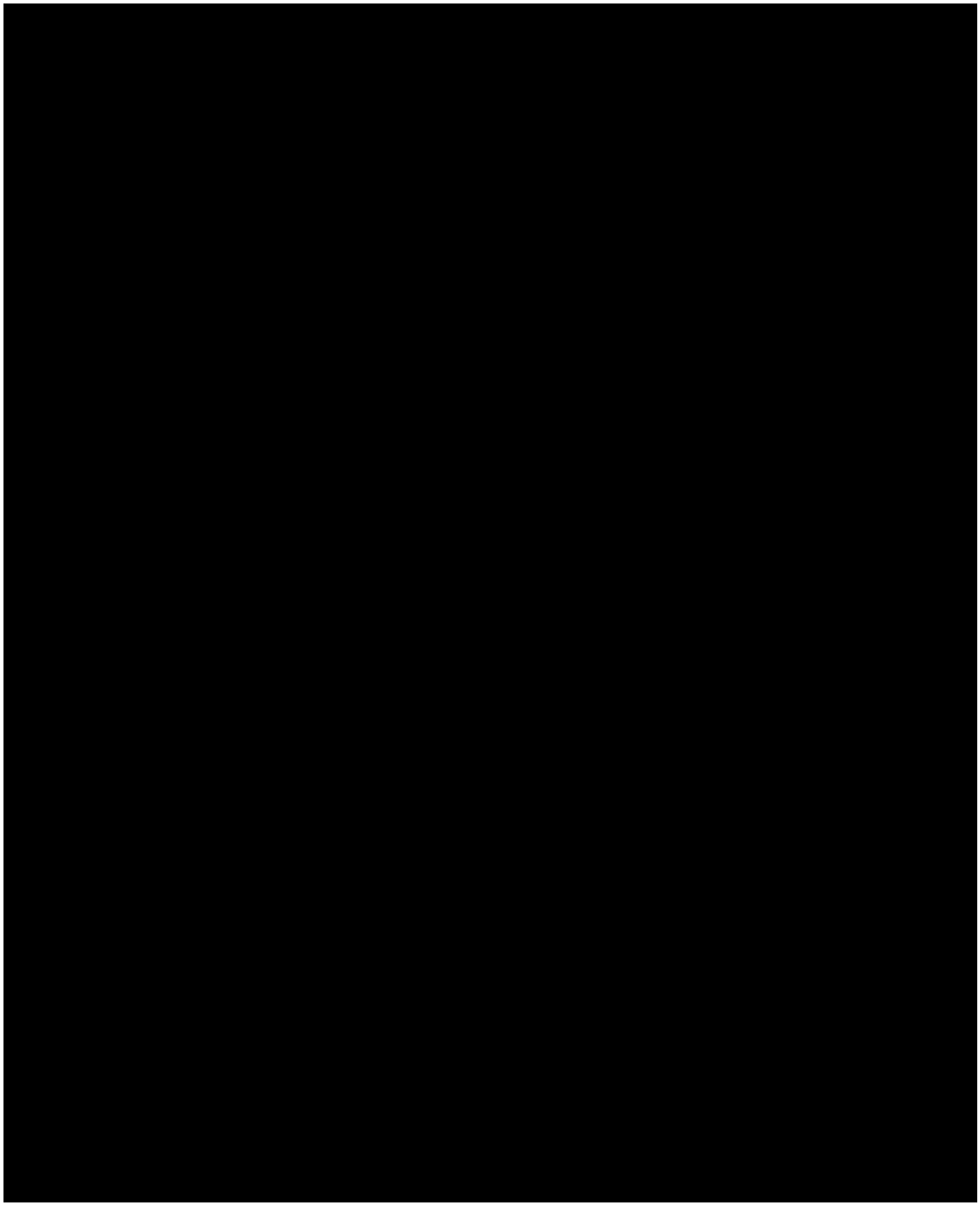
   b. Analysis Phase: The 50 datasets will each be analysed separately, by imputation, to obtain the CMH weighted treatment difference, its associated variance estimation, and the CMH statistic as was produced with the primary endpoint.

      After deriving the percentage of visits with opioid abstinence and the responder status for each participant (Section 5.3.1.1.1) the CMH weighted treatment difference in proportion of responders between treatment groups, its associated variance, and the CMH test statistic will be estimated for each imputation dataset. The CMH statistic, following a Chi-square distribution with degree of freedom =1, will be transformed, s by taking the square root t, as if it is a parameter estimation with the estimated variance= 1 for each imputation.

   c. Pooling Phase: Resulting estimates from Step b will be combined using SAS Proc MIANALYZE to produce final estimates.

      SAS Proc MIANALYZE will then be used to combine the statistics from each iteration in alignment with Rubin's rule (Rubin, 1987). Pooled MI estimations for the treatment group difference (95% CI) as well as the CMH statistic (p-value) will be generated. The p-value associated with the CMH statistic is calculated based on the t-distribution.

See Section 6.4.3 (appendix) for SAS imputation details.



5.3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will be analysed as follows. The analysis of secondary endpoints will use the FAS Population, unless otherwise specified.

5.3.2.1 Secondary endpoint 1: Participants' percentage of days opioids were used out of days assessed (TLFB) over Weeks 10 to Week 38 (inclusive)

5.3.2.1.1 Definition of Endpoint

This endpoint will be summarized as the number of TLFB days opioids were used between the Week 10 visit date and the Week 38 visit date divided by the number of days with observed TLFB information between the Week 10 and Week 38 visits. This time frame includes 15 total assessments from Weeks 10 through 38 including 9 scheduled and 6 planned random visits. The 9 scheduled assessments are at Weeks 10, 14, 18, 22, 26, 30, 34, 36, and 38. The 6 planned random assessments are at Weeks 12, 16, 20, 24, 28, 32. Missing daily TLFB (monotone or intermittent) will not be imputed. For the participant who has an injection of randomised treatment but without any TLFB assessed post-randomisation (typically a rare occurrence), participant's percentage of days opioids were used will be derived based on his/her last observed TLFB assessment prior to the randomisation, i.e., the TLFB for the 7-day opioid use at the randomisation visit or the last observed TLFB after the first injection of RBP-6000 if the TLFB is also missing at the randomisation visit.

Refer to Section 5.3.1.1.1 for details on consideration for missing TLFB results.

5.3.2.1.2 Main analytical approach

A Wilcoxon rank sum test (Van Elteren 1960) stratified for randomisation factors will be performed to compare the difference between the 2 treatment groups. The test result p-value will be used inferentially, if the primary end point test is statistically significant, as described in the multiplicity section above.

Results will include a summary of the mean of participants' percentage of days opioids used (95% CI) for by DB treatment, randomisation strata, and overall. The unadjusted difference (95% CI) between DB treatment group means will be reported overall and within individual stratum.

The CDF for the percentage of days with opioids use will be displayed graphically by DB treatment group, within individual stratum, and overall.

5.3.2.1.3 Supplementary analyses

As with the primary endpoint, a nonparametric randomisation-based covariance analyses will be performed to account for the randomisation strata as a supplementary analysis. The unadjusted and risk-adjusted treatment difference of DB treatment group estimates, 95% CI, and associated p-value will be estimated. There should be no transformation of the outcome, and the weighted estimates of treatment differences should be taken across strata prior to covariance adjustment. Refer to Section 5.3.1.3 for further details.

5.3.2.2 Secondary endpoint 2: Proportion of responders for weekly opioid use over Weeks 10 to 38 (inclusive)

5.3.2.2.1 Definition of Endpoint

The proportion of responders with weekly opioid abstinence ≥ 80% between Weeks 10 to 38 (defined as negative UDS and TLFB for opioid use) will be reported. The percentage of opioid abstinence will be calculated by visit as described in secondary endpoint 3 (Section 5.3.2.1). Under this derivation, any missed or skipped visits will be counted as positive, in accordance with the composite intercurrent event strategy (IES).

The opioid use derivation at a specific visit is described in Section 5.3.1.1.1.

5.3.2.2.2 Analytical approach

Results will include a summary of the proportion of responder outcomes (95% CI) by DB treatment, randomisation strata, and overall. The difference (95% CI) between DB treatment groups will be reported overall and within randomisation strata. The CMH weighted treatment difference with the associated 95% CIs will be reported as with the primary endpoint (Section 5.3.1). A p-value will be reported using a nominal 5% alpha level, without multiplicity adjustments.

The treatment difference in the proportion of responders will be also assessed between DB treatment groups using the unadjusted nonparametric ANCOVA approach accounting for randomisation stratification (Section 5.3.1.3). The difference between treatment groups will be estimated with 95% CI.

5.3.2.3 Secondary endpoint 3: Participants' Percentage of visits with opioid abstinence over Weeks 10 to 38 (inclusive)

5.3.2.3.1 Definition of Endpoint

Participants' percentage of visits with opioid abstinence between Weeks 10 to 38 (inclusive) will be derived as his/her number of visits with negative assessments (defined as negative UDS and TLFB for opioid use) divided by 15. Under this derivation, any missed or skipped visits will be counted as positive, in accordance with the composite intercurrent event strategy (IES).

The opioid use derivation at a specific visit is described in Section 5.3.1.1.1.

5.3.2.3.2 Analytical approach

Results will include a summary of the mean of participants' percentage of abstinent visits (95% CI) for by DB treatment, randomisation strata, and overall. The difference (95% CI) between DB treatment groups will be reported overall and within randomisation strata.

The difference in group mean opioid abstinence percentages will be also compared between DB treatment groups using the unadjusted nonparametric ANCOVA approach accounting for randomisation stratification (Section 5.3.1.3). The difference in the treatment groups' percentages will be estimated with 95% CI.

The CDF for the percentage of visits with opioid abstinence will be displayed graphically by DB treatment group, within individual stratum, and overall.

5.3.2.4 Secondary endpoint 4: Proportion of responders for weekly opioid use for the last 5 visits planned for UDS and TLFB assessment over Weeks 30 to 38 (inclusive)

5.3.2.4.1 Definition of Endpoint

The proportion of responders with weekly opioid abstinence ≥ 80% between Weeks 30 to 38 will be summarized similar to secondary endpoint 2. The opioid abstinence percentage for an individual participant will be derived as his/her number of visits with negative assessments divided by 5. The last 5 visits planned are Weeks 30, 32, 34, 36, and 38. The opioid use derivation at a specific visit is described in Section 5.3.1.1.1.

5.3.2.4.2 Analytic approach

Results will include a summary of the proportion of responders (95% CI) by treatment, randomisation strata, and overall. The unadjusted difference (95% CI) between DB treatment groups will be reported overall and within randomisation strata.

As with the primary endpoint and secondary endpoint 2, The CMH weighted treatment difference with the associated 95% CIs will be reported (Section 5.3.1). Significance testing will not be performed.

The proportion of responders will be compared between treatment groups using the unadjusted nonparametric ANCOVA approach accounting for randomisation stratification (Section 5.3.1.3). The treatment difference in the proportion of responders will be estimated with 95% CI.

5.3.2.5 Secondary endpoint 5: Proportion of responders for daily opioid use for the last 5 visits with observed TLFB post randomisation

5.3.2.5.1 Definition of Endpoint

The responders for the daily opioid use will be based on the 7-daily TLFBs for the prior week collected at the last 5 observed visits post randomisation. The opioid use percentage for an individual participant will be derived as his/her number of days that opioids were used divided by the number of days with observed TLFB information at those 5 visits post randomisation. A participant with ≤ 20% opioid use (> or =80% abstinence) will be classified as a responder, otherwise as a nonresponder. The participant without observed daily TLFB will also be classified as a nonresponder.

For participants who have fewer than 5 visits with observed TLFB post randomisation, all available daily TLFB information will be used to derive the opioid use percentage. No missing data will be imputed according to the while-on-treatment IES.

5.3.2.5.2 Analytic approach

Results will include a summary of the proportion of responder outcomes (95% CI) by treatment, randomisation strata, and overall. The unadjusted difference (95% CI) between DB treatment groups will be reported overall and within randomisation strata.

As with the primary endpoint and secondary endpoint 2, The CMH weighted treatment difference with the associated 95% CIs will be reported (Section 5.3.1). Significance testing will not be performed.

The proportion of responders will be compared between treatment groups using the unadjusted nonparametric ANCOVA approach accounting for randomisation stratification (Section 5.3.1.3). The treatment difference in the proportion of responders will be estimated with 95% CI.

5.3.2.6 Secondary endpoint 6: Participants' percentage of visits with opioid abstinence (defined as negative UDS and TLFB for opioids use) overall (Weeks 2 to 38 inclusive)

5.3.2.6.1 Definition of Endpoint

The opioid abstinence percentage for an individual participant will be derived as his/her number of visits with negative assessments divided by 23 (the number of the planned visits for opioid use assessments over Weeks 2 to 38). The 23 visits include 17 scheduled assessments at Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 18, 22, 26, 30, 34, 36, and 38 as well as 6 planned random assessments at Weeks 12, 16, 20, 24, 28, and 32. Under this derivation, any missed or skipped visits will be counted as positive in accordance with the composite intercurrent event strategy (IES). The opioid use derivation at a specific visit is described in Section 5.3.1.1.1

5.3.2.6.2 Analytic approach

Results will include a summary of the mean of participants' percentage of abstinent visits (95% CI) by DB treatment, randomisation strata, and overall. The unadjusted difference (95% CI) between DB treatment groups will be reported overall and within randomisation strata.

The group mean of the percentages will be compared between treatment groups using the unadjusted nonparametric ANCOVA approach accounting for randomisation stratification (Section 5.3.1.3). The difference in the treatment groups' percentages will be estimated with 95% CI.

The CDF of the percentage of visits with opioid abstinence will be displayed graphically by DB treatment group, within individual stratum, and overall.

5.3.2.7 Secondary endpoint 7: Participants' percentage of days opioids were used out of days assessed (TLFB) overall (Weeks 2 to 38 inclusive)

5.3.2.7.1 Definition of Endpoint

Participants' percentage of days that opioids were used out of days assessed (TLFB) over Weeks 2 to 38 (inclusive) will be based on the 7-daily TLFB for the prior week collected at the 17 scheduled and 6 planned random visits. The 23 visits include 17 scheduled assessments at Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 18, 22, 26, 30, 34, 36, and 38 as well as 6 planned random assessments at Weeks 12, 16, 20, 24, 28, and 32. The overall opioid use percentage for an individual participant will be derived as his/her number of days of opioid use divided by the number of days with observed TLFB information, according to the while-on-treatment IES. Refer to Section 5.3.1.1.1 for the derivation/imputation of opioids use from the TLFB.

5.3.2.7.2 Analytic approach

Results will include a summary of the mean of participants' percentage of days that opioids were used out of days assessed (95% CI) by DB treatment, randomisation strata, and overall. The unadjusted difference (95% CI) between DB treatment groups will be reported overall and within randomisation strata.

The group mean of the percentages will be compared between treatment groups using the unadjusted nonparametric ANCOVA approach accounting for randomisation stratification (Section 5.3.1.3). The difference in the treatment groups' percentages will be estimated with 95% CI.

5.3.2.8 Secondary endpoint 8: Participants' percentage of days opioids were used via the injection route out of days assessed (TLFB) over Weeks 10 to 38 (inclusive)

5.3.2.8.1 Definition of Endpoint

The percentage of days participants used opioids via the injection route will be summarized for the Injecting Opioid Participants subgroup as defined in Section 5.1.6. The overall opioid use percentage for an individual participant will be derived as his/her number of days of opioid use via injection ("Yes") divided by the number of days with TLFB information, according to the

while-on-treatment IES. Refer to Section 5.3.1.1.1 for the derivation/imputation of opioids use from the TLFB.

5.3.2.8.2 Analytic approach

Results will include a summary of the mean of participants' percentage days opioids were injected between Weeks 10 and 38 (95% CI) by DB treatment, randomisation strata, and overall. The unadjusted difference (95% CI) between DB treatment groups will be reported overall and within randomisation strata.

The group mean of the percentages will be compared between treatment groups using the unadjusted nonparametric ANCOVA approach accounting for randomisation stratification (Section 5.3.1.3). The difference in the treatment groups' percentages will be estimated with 95% CI.

5.3.2.9 Secondary endpoint 9: Average number of times opioids were used per week (TLFB) by visit

5.3.2.9.1 Definition of Endpoint

The average number of times opioids were used per week (TLFB) for a given visit within a treatment group will be based on the daily TLFBs for the prior week collected at that visit, and calculated as the number of times opioids were used divided by the number of days with observed TLFB information for all participants within the group for that visit, then times 7. Primarily, the number of times that a participant uses opioids daily will not be imputed if missing or if the result appears far outside of a normal range as a likely error.

The study visits from Screening to Week 38 include 19 scheduled assessments at Screening and Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 18, 22, 26, 30, 34, 36, and 38 as well as 6 planned random assessments at Weeks 12, 16, 20, 24, 28, and 32.

5.3.2.9.2 Analytic approach

The average value for each treatment group will be summarised by visit overall and within individual randomisation stratum; the unadjusted difference between treatment groups will be estimated with a 95% CI for each visit overall and within each randomisation stratum. A figure will be plotted to display the average number of times opioids were used at each visit by DB treatment group and overall.

As a sensitivity analysis to assess the potential impact of erroneous data entry, results will be repeated while imputing to missing single TLFB daily 'number of times used' values that are >30 and where the percent difference in number of times used between that value and the next highest value of times used for that participant is >50%.

Participants reporting outlier opioid use for the number of times used, that is single daily number of times used >30, will have their full TLFB report of the daily number of times used summarized graphically by visit via a participant-specific spaghetti plot where each visit from

Week 1 Day 1 to Week 38 will be represented by a different line across the 7 days of the TLFB on the x-axis.

5.3.2.10 Secondary endpoint 10: Change in participants' number of times opioids were used per week from Screening or DB Randomisation baseline to each visit

5.3.2.10.1 Definition of Endpoint

The change in participants' number of times opioids were used per week from Screening or DB Randomisation Baseline to each visit will be based on the 7-daily TLFB for the prior week collected at that visit. A "while-on-treatment" strategy will be used to address IEs, in that only the participants with complete 7-daily TLFB information for a given visit will be analysed for that visit.

The study visits from Screening to Week 38 include 19 scheduled assessments at Screening and Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 18, 22, 26, 30, 34, 36, and 38 as well as 6 planned random assessments at Weeks 12, 16, 20, 24, 28, and 32. The visits from DB Randomisation to Week 38 include 13 scheduled assessments at Weeks 6, 7, 8, 9, 10, 14, 18, 22, 26, 30, 34, 36, and 38 as well as 6 planned random assessments at Weeks 12, 16, 20, 24, 28, and 32. The change from DB Randomisation Baseline (Week 6) will be calculated from Weeks 6 to 38. The change from Screening (pre-BUP treatment baseline) will be calculated from Weeks 1 to 38.

5.3.2.10.2 Analytic approach

The mean change value and percentage change value from Screening or DB Baseline for each treatment group will be summarised by visit, overall, and within individual randomisation stratum; the difference between DB treatment groups will be estimated with a 95% CI for each visit overall and within each randomisation stratum.

In the above main analytic approach, only the participants with complete 7-daily TLFB information for a given visit will be analysed for that visit. As an alternative approach to handle missing data, a sensitivity analysis will include participants with incomplete or partial daily TLFB information at the visit. TLFB information that is only partially complete at a given visit will be imputed as the number of times opioids were used in total for that participant that divided by the number of days with observed TLFB information times 7 for that visit.

5.3.2.11 Secondary endpoint 11: Proportion of participants abstinent (defined as negative UDS and TLFB for opioid use) by visit

5.3.2.11.1 Definition of Endpoint

The proportion of participants abstinent (defined as negative UDS and TLFB for opioid use) for a given visit within a treatment group will be calculated as the number of participants abstinent (derived according to Section 5.3.1.1.1) divided by the number of participants with observed opioid use assessment for that visit. Refer to Section 6.4 (appendix) for the derivation of UDS

opioids use. Refer to Section 6.4 (appendix) for the derivation/imputation of opioids use from TLFB.

The study visits from Screening to Week 38 include scheduled assessments at Screening, Week 1 Day 1, and Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 18, 22, 26, 30, 34, 36, and 38 as well as planned random assessments at Weeks 12, 16, 20, 24, 28, and 32.

5.3.2.11.2 Analytic approach

Results will include a summary of the proportion of abstinent participants for each treatment group by visit from Screening to Week 38 overall and within individual randomisation stratum; the unadjusted difference (95% CI) between DB treatment groups will be estimated for each visit overall and within individual randomisation stratum. If proportions are 0% or 100%, the exact Clopper-Pearson CI will be used.

Participants' overall TLFB and UDS opioid use will be also summarized separately in a graphical heatmap (Green=Negative, Orange=Positive, White=Missing) by visit in order of descending percentage abstinence.

5.3.2.12 Secondary endpoint 12: Average number of days opioids were used per week (TLFB) by visit

5.3.2.12.1 Definition of Endpoint

The average number of days that opioids were used per week (TLFB) for a given visit within a treatment group will be calculated as the number of days that opioids were used divided by the number of days with observed TLFB information for all participants within the group for that visit, then times 7. No imputation for missing data will be performed in accordance with a while-on-treatment IES.

The study visits from Screening to Week 38 include 19 scheduled assessments at Screening and Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 18, 22, 26, 30, 34, 36, and 38 as well as 6 planned random assessments at Weeks 12, 16, 20, 24, 28, and 32.

5.3.2.12.2 Analytic approach

The average number of days that opioids were used per week (TLFB) for each treatment group will be summarised by visit from Screening or randomisation to Week 38 for overall and within individual randomisation stratum; the difference between treatment groups will be estimated with a 95% CI for each visit.

5.3.2.13 Secondary endpoint 13: Treatment retention since DB Randomisation

5.3.2.13.1 Definition of Endpoint

The treatment retention since DB Randomisation will be estimated using the Kaplan Meier method. The event in consideration will be prematurely discontinuing the study prior to Week 38/EOT Visit. The time to the event will be calculated in days as the date of the last scheduled visit observed during the DBTP minus the date of DB Randomisation +1. Participants who complete the study will be censored administratively at the Week 38/EOT Visit, and the corresponding censor time will be calculated as the date of Week 38/EOT Visit minus the date of Randomisation +1. As no dates are expected to be missing, missing data are not applicable for this endpoint.

5.3.2.13.2 Analytic approach

The endpoint will be presented by treatment group overall and within individual randomisation stratum using a Kaplan-Meier curve. Retention rate (95% CI) at 32 weeks post DB Randomisation (Week 38 EOT) will be estimated using the number of participants who completed the study divided by the number of randomised participants by treatment group overall and within the individual randomisation stratum. If percentages are 0% or 100%, the exact Clopper-Pearson CI will be used.

5.3.2.14 Secondary endpoint 14: Proportion of randomised participants who complete the last scheduled injection of RBP-6000

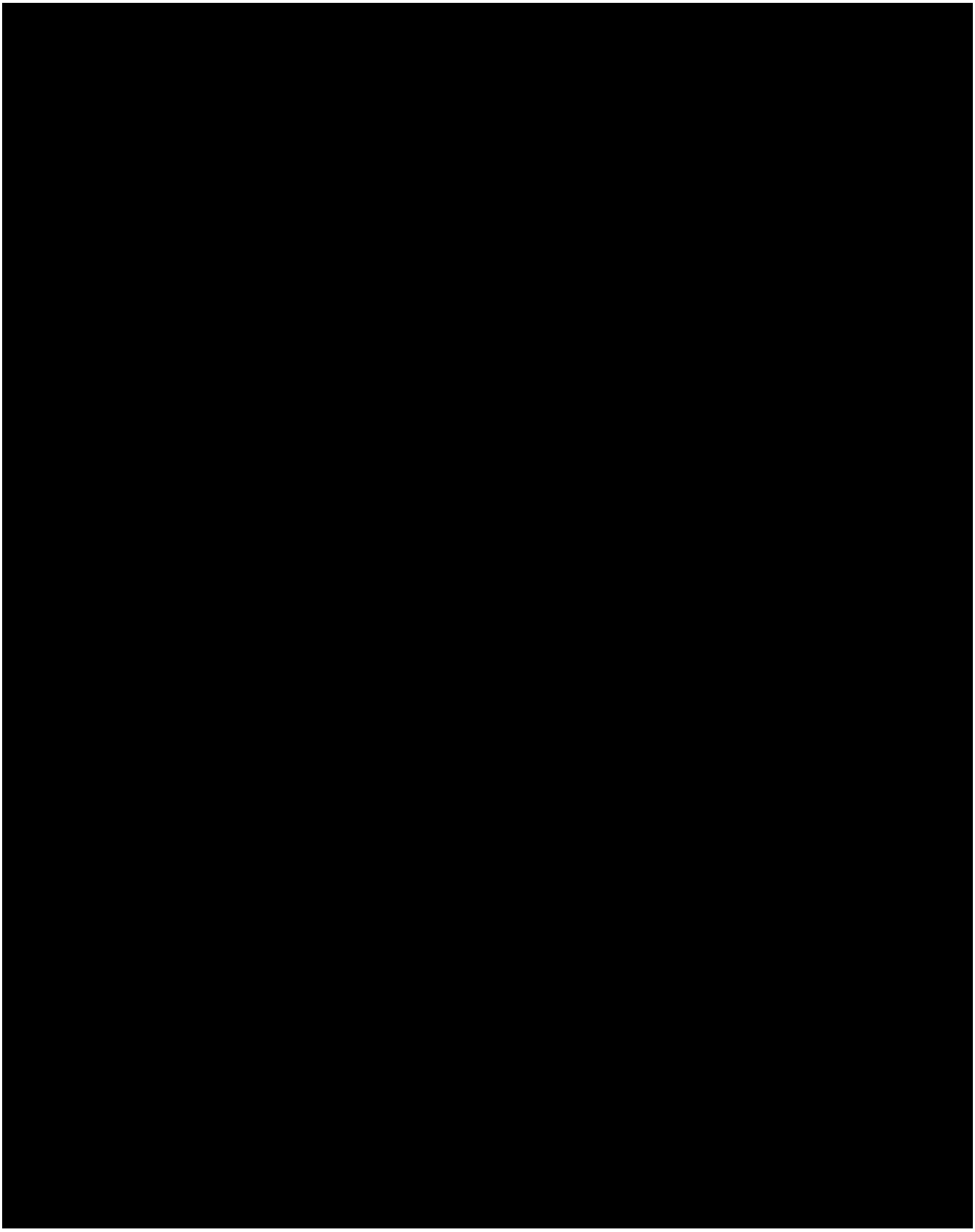
5.3.2.14.1 Definition of Endpoint

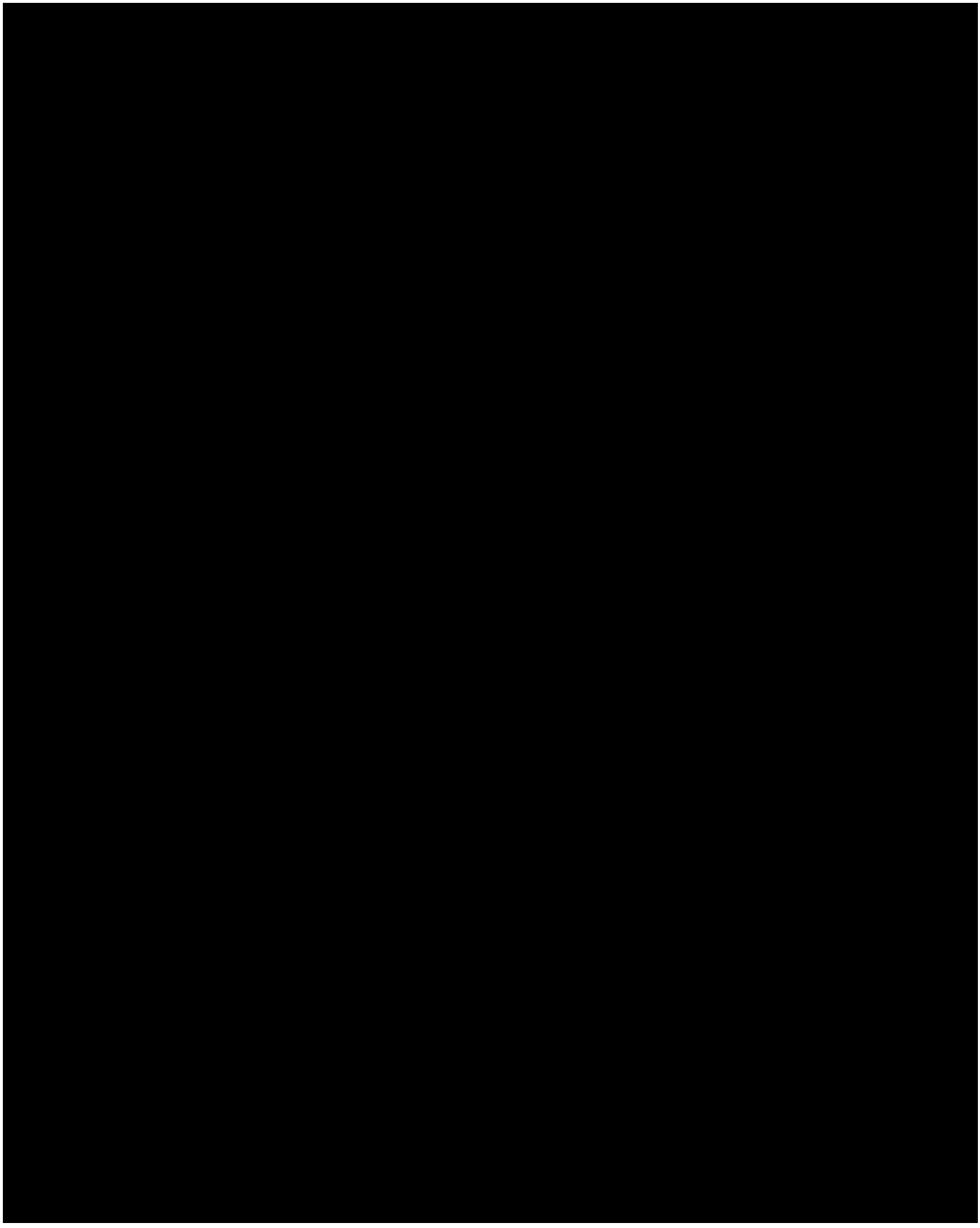
The proportion of randomised participants who complete the last scheduled injection of RBP-6000 at Week 34 will be summarized using observed data. Missing data are not applicable for this endpoint.

5.3.2.14.2 Analytic approach

Results will include descriptive statistics overall, by treatment, and within individual randomisation stratum. The unadjusted difference between treatment groups will be estimated with 95% CI.

The proportion of participants who complete the last scheduled RBP-6000 injection will be compared between treatment groups using the unadjusted nonparametric ANCOVA approach accounting for randomisation stratification (Section 5.3.1.3). The difference in proportions between DB treatment groups will be estimated with 95% CI. If proportions are 0% or 100%, the exact Clopper-Pearson CI will be used.





5.3.4 Analysis of Subgroups

The primary endpoint result of the CMH weighted difference in proportion of responders (Weeks 20-38) between the RBP-6000 300-mg and 100-mg treatment groups (95% CI) as well as the first secondary endpoint of the group mean difference in DB treatment (95% CI) in participants' percentage of TLFB days opioids were used out of days assessed (Weeks 10-38) will also be presented for each of the following groups listed in Section 5.1.6:

- Black/African American vs Non-Black/African American
- Opioid injecting participants
- High-dose opioid use
- Fentanyl use

- Opioid (other than fentanyl) use
- Multiple drug use vs Opioid only use
- Double-blind Completers
- Injection Compliant Participants

There will be no formal comparison or contrast between treatments nor between randomisation strata for any subgroupings. Forest plots will be presented to display the results for subgroup analyses in a visual manner.

5.4 Safety Analyses

Safety data will be analysed using descriptive statistics for continuous endpoints and frequency counts with percentages for categorical endpoints, using an “as observed” approach.

All safety summaries will be presented both for the DB Safety and OL Safety Populations. OL Safety summaries will include results collected from the Week 1 Day 1 RBP-6000 injection to the last EOS Visit unless otherwise noted. DB Safety summaries will include results collected from the Week 6 RBP-6000 injection to the last EOS Visit.

All laboratory results, ECG results, and vital signs will be reported based on the nominal visit. If multiple records exist for a single visit, the earliest will be used. Unscheduled visit results will be listed.

AEs 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 (WHODD). See Sections 6.4.4, 6.4.5, 6.4.6, and 6.4.7 (appendices) for details on imputation for missing adverse event or concomitant medication dates. Dictionary versions and additional details of the coding process are described in the Data Management Plan.

5.4.1 Extent of Exposure

For the both the OL Safety and DB Safety Populations, the following exposure parameters will be summarized by RBP-6000 maintenance dosage group (100-mg vs 300-mg) and overall:

- The total number of injections for each participant
- The number and percentage of participants who received RBP-6000 at each planned injection (1-10),
- The cumulative frequency of injections of RBP-6000 (3-10).
- The total amount of time on RBP-6000 treatment (days) as calculated:
    - OLTP: Date of Week 6 injection – date of initial injection + 30.
    - DBTP: Date of final injection – date of Week 6 injection + 30.

- Overall: Date of final injection – date of initial injection + 30.

- The number (proportion) of participants who took concomitant TM buprenorphine (captured in the concomitant medication CRF page) during the OLTP, DBTP, and Overall. The number of participants who took TM buprenorphine and did not continue to the DBTP will also be summarized for the OL Safety Population.
- The number of times concomitant TM buprenorphine was taken the OLTP, DBTP, and Overall.

A summary of the number of days between injections will also be presented. Injection intervals will be shown starting from the Week 1 Day 1 injection (OL Safety Population) or the Week 6 Injection (DB Safety Population) and summarized with descriptive statistics. The number of participants receiving an early or late injection per protocol will also be summarized (target 28 days, -2/+14). Injections will be counted as they are numbered in the order that they are administered and not assigned to a visit. There will be no summary of "missed" injections.

Note, if participants received the wrong maintenance dosage at a certain injection, the number and percentage of participants who received their randomised maintenance dosage will also be summarised.

If a participant records any visit without receiving an injection, all of their visits with associated injection datetimes will be listed.

5.4.2 Adverse Events

Treatment-emergent adverse events (TEAEs) will be presented using categorical counts and percentages. Treatment columns will be displayed based on the population as described in Section 5.1.4. A TEAE will be considered treatment emergent for the OL Safety Population if it starts on or after the date/time of the first RBP-6000 injection on Week 1 Day 1. A TEAE will be considered treatment-emergent for the DB Safety Population if it starts on or after the date/time of the Week 6 RBP-6000 injection.

AEs will be coded using MedDRA and grouped by system organ class (SOC). 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.

5.4.2.1 Adverse Event Summary Categories

The number and percentage of participants with reported TEAEs will be tabulated in the following sequences:

- by SOC and preferred term (PT)
- by PT
- by severity, SOC, and PT

If the same PT is recorded more than once for a participant, the participant will be counted only once for that PT using the most severe occurrence in summarisation by severity.

Tabulations will be presented for following categories of TEAEs in an overall summary in addition to breakdowns by SOC and PT:

- Any TEAE; by severity, SOC, and PT
- Severe; by SOC and PT
- Serious; by SOC and PT
- Drug-related to RBP-6000; by severity, SOC, and PT
- Leading to treatment discontinuation from RBP-6000 (action taken is "Drug withdrawn" per eCRF); by severity, 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
  - Hepatic disorders per the Customised MedDRA Query (CMQ) definitions (Table 21); by SOC and PT
  - Injection site reaction events, per the CMQ definitions (Table 22); by SOC and PT
- Reported as opioid withdrawal symptom, by SOC and PT

The overall AE summary table for the DB Safety Population will also include an estimate of the DB randomised treatment group difference with 95% CI will be estimated by Miettinen-Nurminen method with/without accounting for randomisation stratification.

An overall summary of OLTP specific TEAEs will also be presented separately for both the OL Safety and DB Safety Populations. These TEAEs will be considered treatment-emergent if they start after the datetime of the first RBP-6000 injection but not after the 3rd third RBP-6000 injection at Week 6.

5.4.2.2 Adverse Events of Special Interest

A single AE of special interest, the "Removal of drug depot", will be summarized specifically by treatment group and overall.

5.4.2.3 TEAE by Injection, Injection interval, and Exposure Adjustment

The percentage of participants reporting TEAEs will also be presented considering exposure at all Injection intervals. All TEAEs, Serious, Severe, RBP-6000 related, Leading to treatment discontinuation, Injection Site Reactions, Hepatic Disorders, and Opioid Withdrawal Symptom TEAEs will be reported for the following exposure categories (see below). TEAEs will be counted as being in an interval category if they start between the listed injection dates in the specific category (eg, Injection 1 (Week 1 Day 1) date/time ≤ AE start date < Injection 2 date/time, Week 2 injection date/time ≤ AE start date < Injection 3 date/time etc.). The number of injections administered will be displayed alongside the TEAEs.

- Individual RBP-6000 injection intervals for all injections from Week 1 Day 1 to Week 38/EOT
- RBP-6000 Injections 1-3
- RBP Injections 3-6
- RBP Injections 6-10

The number of participants reporting TEAEs (or the individual TEAE categories described in the pervious paragraph) per 100 administered injections will be calculated by DB treatment group for the DBTP and the Overall RBP-6000 Treatment Period.

The percentage of participants reporting an injection site reaction for each injection will also be displayed graphically in a histogram for each injection interval (eg, 1-2, 2-3, 3-4, etc.).

5.4.3 Height, Weight, and Body Mass Index

Values and change from Screening Baseline will be summarized descriptively using descriptive statistics for participant weight and BMI at each nominal scheduled visit. Height will be summarized at the Screening Visit only. The collection visits for weight and BMI include Screening and Weeks 2, 6, 10, 14, 18, 22, 26, 30, 34, 36, and 38/EOT. Height, weight, and BMI will be listed.

5.4.4 Vital Signs

Vital sign values (collected pre-injection) as well as change from Screening Baseline including systolic blood pressure, diastolic blood pressure, pulse rate, and respiratory rate collected at each nominal scheduled visit will be summarised using descriptive statistics.

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

The collection visits include Screening, Week 1 Day 1 (the day of injection 1), and Weeks 2, 3, 4, 5, 6, 10, 14, 18, 22, 26, 30, 34, 36, and 38/EOT.

5.4.5 Electrocardiograms

Electrocardiogram (ECG) numeric variables (heart rate, PR interval, QRS duration, QT interval, and QT interval corrected using Fridericia's method) will be summarised using descriptive statistics for each nominal visit. Participants with QTcF >500 and QTcF change from Screening or DB Baseline to Week 38 (EOT)/ET will be summarized.

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

The collection visits include Screening, Week 1 Day 1 (the day of injection 1), and Weeks 2, 4, 6, and 38/EOT.

5.4.6 Liver Function Tests

Results of liver function tests (LFT) including parameters of interest (ALT, AST, ALP, total bilirubin, albumin, total protein, gamma glutamyl transferase, and lactase dehydrogenase) will be summarised at each nominal visit using descriptive statistics. The LFT visits include Screening and Weeks 1, 2, 6, 10, 14, 18, 22, 30, and 38/EOT. Change values from Pre-OL Injection Baseline

will be presented for the OL Safety population and from Pre-DB Injection Baseline for the DB Safety population.

Parameters of interest (as mentioned above) will also be summarised in reference range shift tables to display screening value vs last assessment on treatment. The standard categories will be used for the shifts (e.g., low/normal/high and missing, if applicable).

The number and percentage of participants meeting liver function test criteria (as described below) will be summarised. For each listed laboratory parameter, the participant will be counted only once according to his/her worst grade (highest result).The criteria are factors of the upper limit of normal (ULN) for ALT, AST, and total bilirubin, as follows:

a. AST or ALT >3xULN and total bilirubin >2xULN
b. ALT (>3xULN)
    - ≥8xULN
    - ≥5xULN to <8xULN
    - >3xULN to <5xULN
c. AST (>3xULN)
    - ≥8xULN
    - ≥5xULN to <8xULN
    - >3xULN to <5xULN
d. Total Bilirubin (>2xULN)
    - ≥ 5xULN
    - >2xULN to <5xULN
e. Both ALT >3xULN and AST >3xULN

An eDISH plot displaying Maximum total Bilirubin by Maximum ALT will also be produced. LFT test results and criteria specifications (including AST, ALT, GGT, ALP, Bilirubin and the associated lab collection dates) will be listed for participants with values meeting any of the above criteria.

5.4.7 Laboratory Tests (Serum Chemistry, Haematology, and Urinalysis)

The results of scheduled assessments of laboratory tests will be summarised for the Chemistry and Haematology lab categories at each visit. The visits for the assessments of laboratory tests (haematology, chemistry, and urinalysis) include Screening, and EOT (Week 38) or ET Visit (whichever is applicable).

Unless otherwise specified, all continuous laboratory data will be summarised using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for each scheduled study assessment by parameter class (haematology, chemistry). Shifts in Chemistry and Haematology lab parameters will also be summarised as available in shift tables. Screening value vs EOT/ET will be displayed separately in categories of low, normal, high, and missing as applicable by grade.

Urinalysis results will be listed.

5.4.8 Concomitant Medications

The number and percentage of participants taking any prior medication and concomitant medication will be summarised by pharmacological group (ATC level 3) and preferred drug name using descriptive statistics (see Section 6.5 [appendix] for prior and concomitant derivations). Prior medication and concomitant medications for the OLTP, the DBTP, and the whole study treatment duration (OLTP+DBTP), defined in Section 6.5 [appendix], will be summarised.

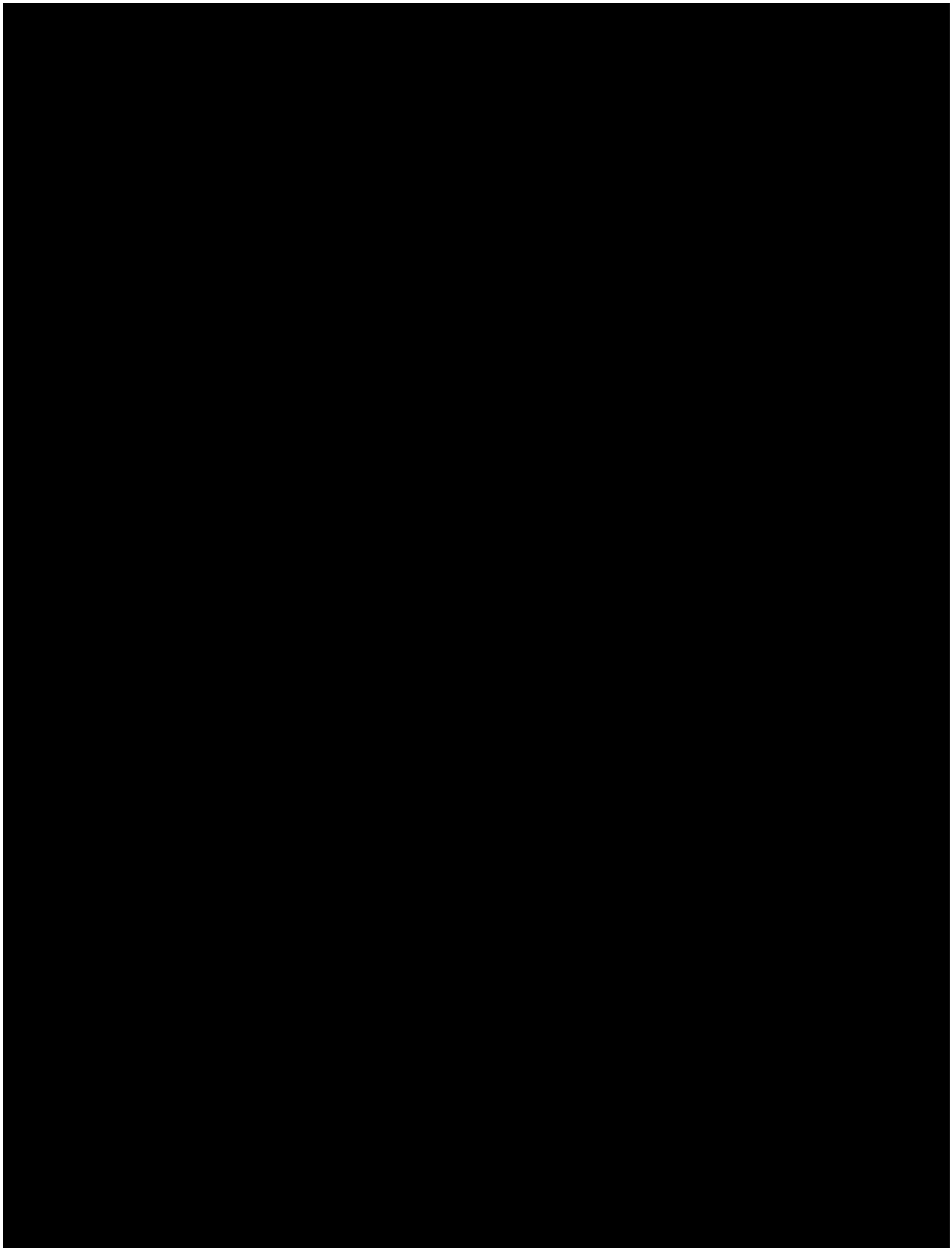
Concomitant medications will be coded using the WHODD.

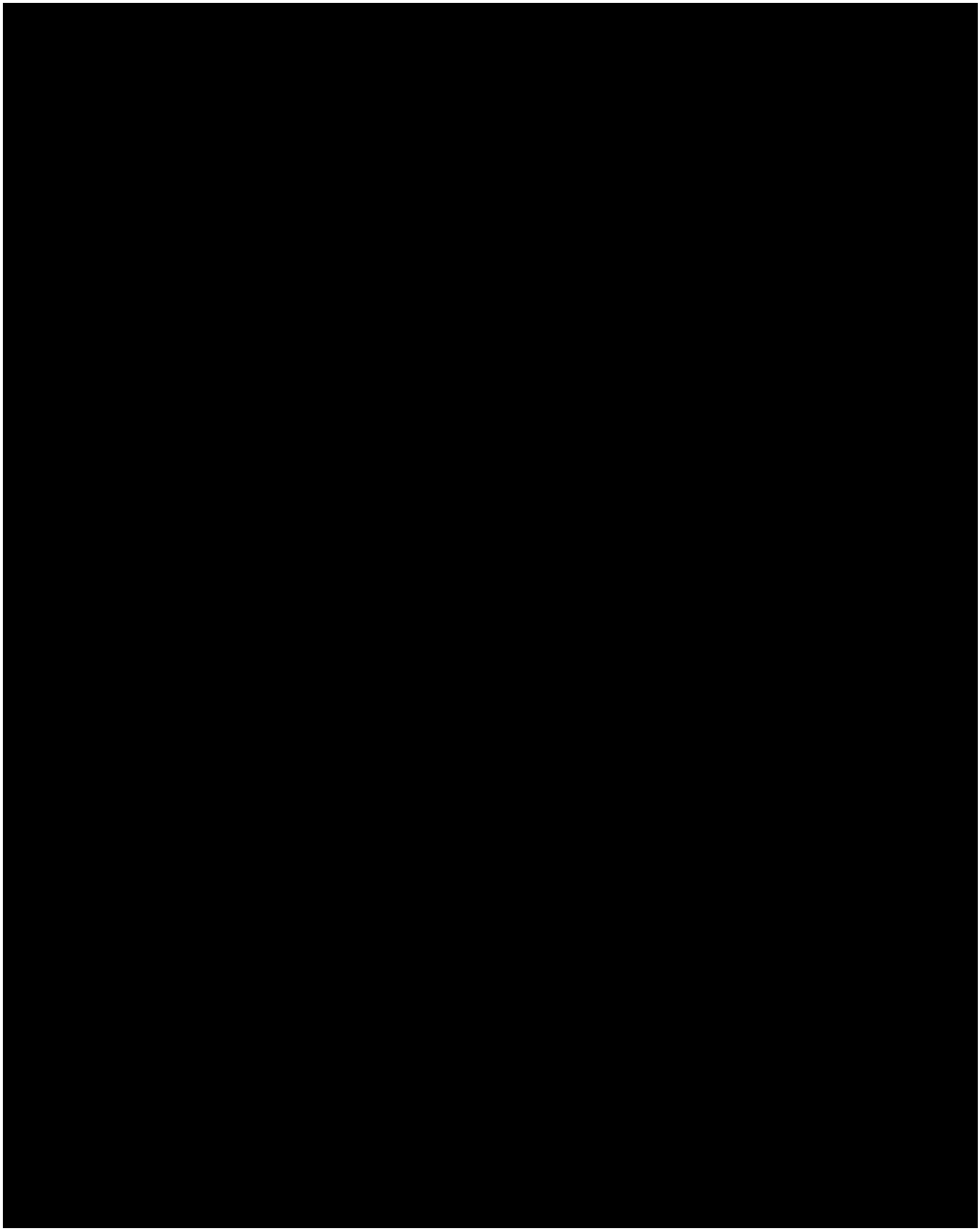
5.4.9 Pregnancy

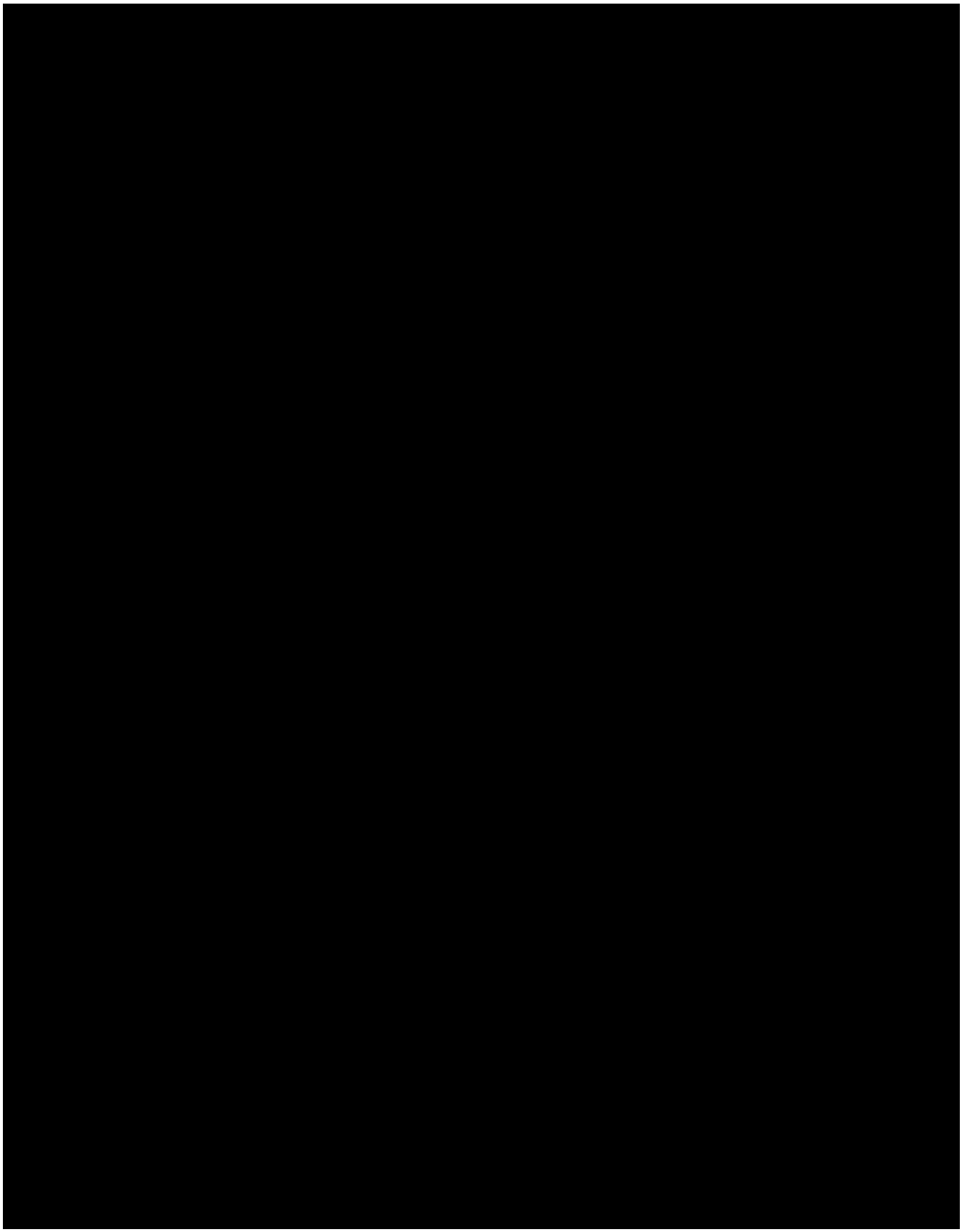
Urine pregnancy results will be listed for each visit if applicable. A listing of all available labs for pregnant participants will be produced as well. The study visits for urine pregnancy testing include Screening and Weeks 1, 2, 6, 8, 10, 14, 18, 22, 26, 30, 34, and 38.

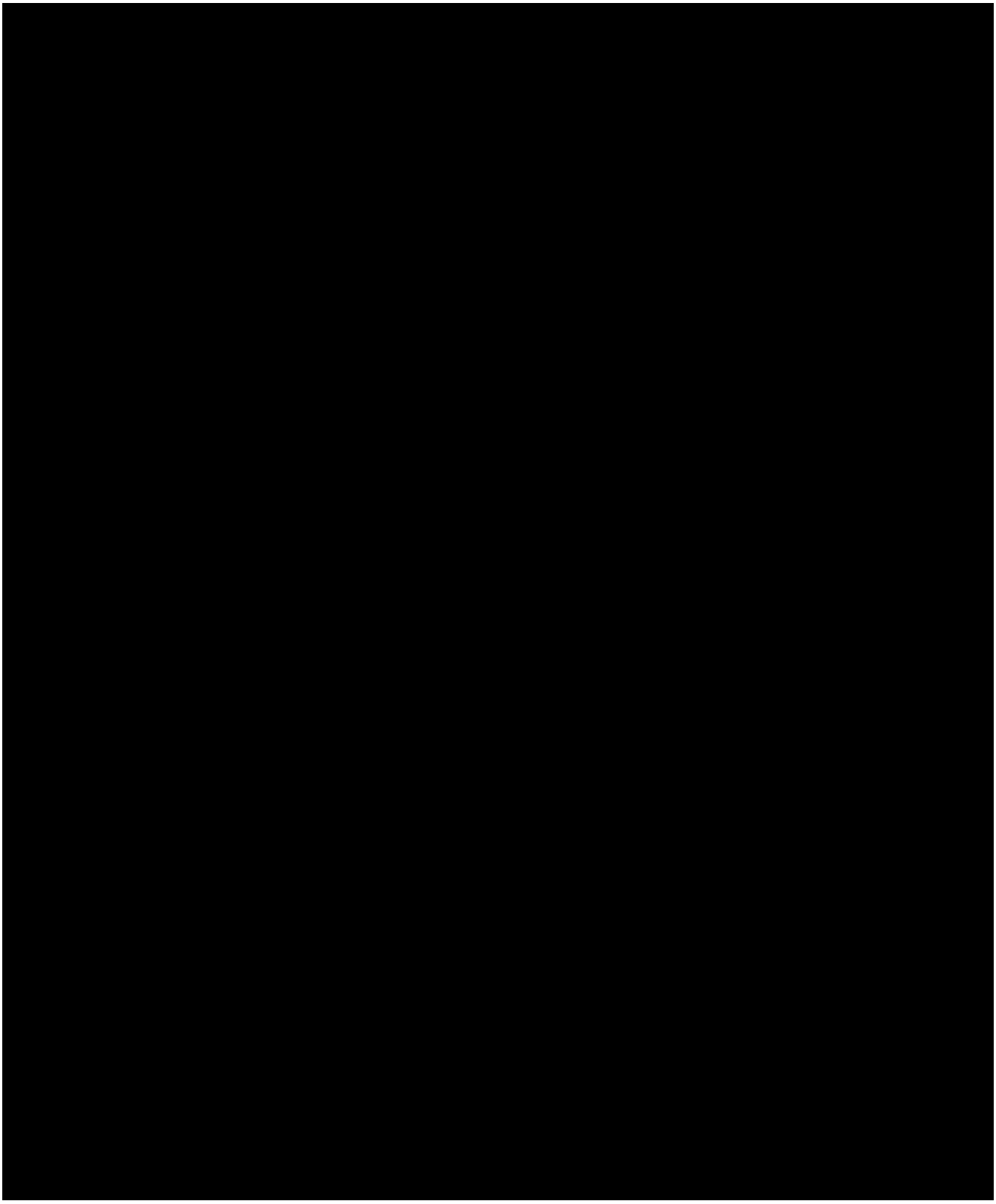
5.4.10 Other Safety Variables

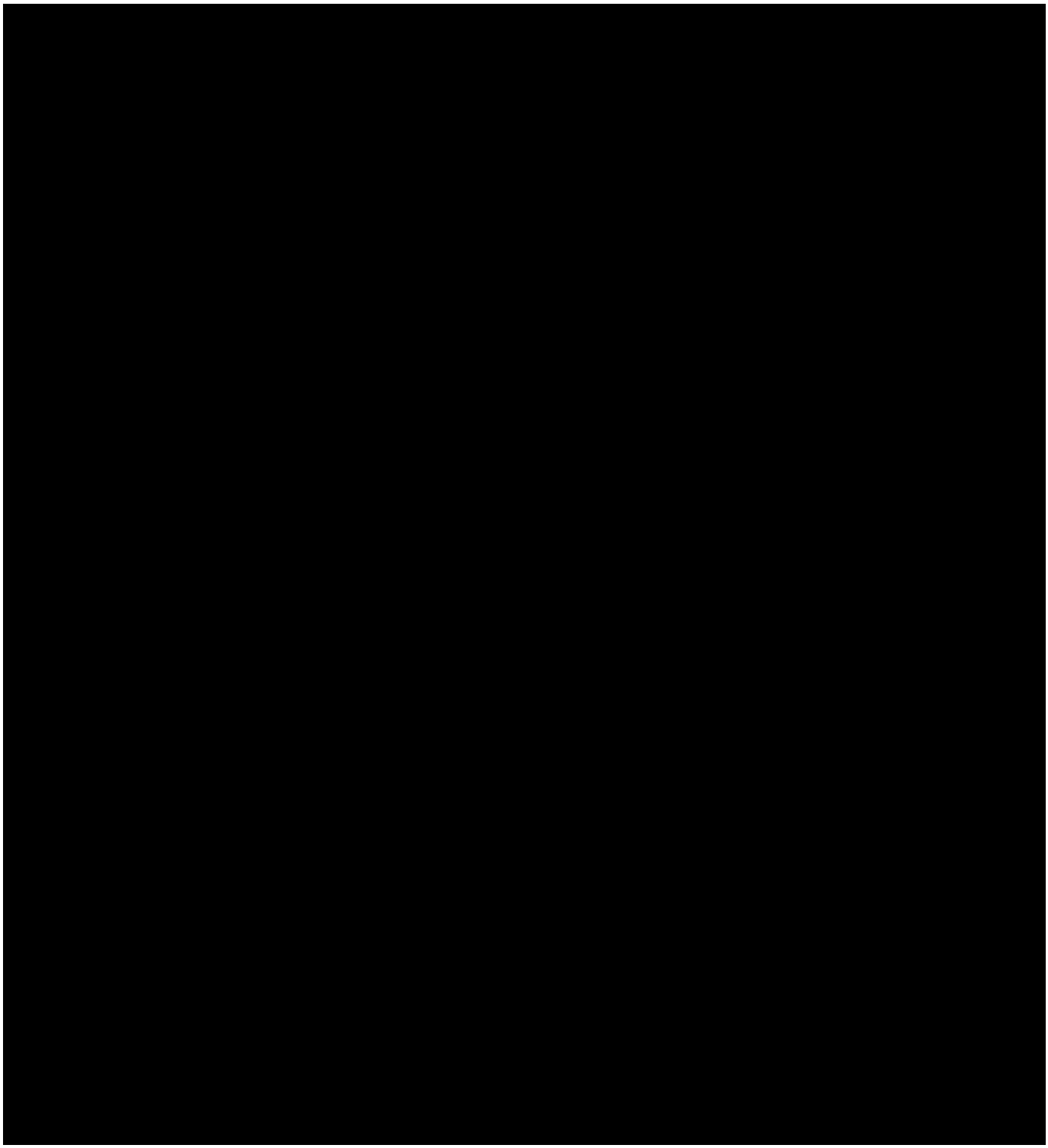
The HIV 1/HIV 2, hepatitis B, and hepatitis C antibody testing will be conducted at Screening in the absence of a positive (documented) medical history for these conditions and will be performed at EOT/ET only if the participant was negative at Screening. The number of participants with negative results at Screening will be summarised by treatment group and overall. Additionally, the number of participants and proportion of negative/positive results at EOT/ET will be summarised for the participants with negative result at Screening. Results of these tests will be additionally listed.











5.7 Interim Analyses

No interim analyses are planned for the main study.

6 APPENDICES: SUPPORTING DOCUMENTATION

6.1 List of Abbreviations

Table 16. List of Abbreviations

Abbreviation	Definition
Abs	Absolute
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
BA	bioavailability
BAC	balanced-across-centres
BE	bioequivalence
BLQ	below the limit of quantitation
BOCF	baseline observation carried forward
BP	blood pressure
BUP	buprenorphine
CDF	Cumulative Distribution Function
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COWS	Clinical Opiate Withdrawal Scale
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DB	Double-blind
DBTP	randomised Double-blind Treatment Period
DMC	data monitoring committee
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
E DMC	external data monitoring committee
EOS	end of study
EOT	end of treatment
FAS	full analysis set
FET	Fisher's exact test
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GLIMMIX	generalised linear mixed-effects model with repeated measures
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
[redacted]	
ICD	informed consent document
ICF	Informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	internal review committee
ISO	International Organization for Standardization
IST	independent statistical team
ITT	intent-to-treat
IXRS/IWRS	Interactive Voice/Web Response System
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LOD	limit of detection
LS	least-squares
LSM	least-squares mean
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple Imputation
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measures
MNAR	missing not at random
MOUD	medications for opioid use disorder
N/A	not applicable
NEAE	newly emergent adverse event
NNB	number needed to benefit
NNH	number needed to harm
NNT	number needed to treat
NOAEL	no-observed-adverse-effect level
[redacted]	
OL	Open-label
OLIS	Open-label Induction Sub-study
OLTP	Open-label Treatment Period
OUD	opioid use disorder
PCS	potentially clinically significant
[redacted]	
PP	per-protocol
PRO	patient-reported outcome
PT	preferred term
Q1	25% quartile
Q3	75% quartile
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RCDC	reverse cumulative distribution curve
RF	randomisation factor
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

Abbreviation	Definition
SE	standard error
SOC	System Organ Class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TLF	tables, listings and figures
TM	transmucosal
UDS	urine drug screen
ULN	upper limit of normal
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

6.2 Changes to Protocol-Planned Analyses

- Due to an internal update to the company writing style guide, text transferred as a reference from the protocol has been updated for minor adjustments to formatting, abbreviations, as well as common reference terms.
- Estimands were edited to match the current language in the analysis plan. Specifically, the primary endpoint composite strategy was clarified to assume all missing/skipped visits are considered non-negative, and thus, not opioid abstinence. While the analysis treats the value as if it were positive, the value of positive is not imputed.
- The Full Analysis Set (FAS) definition was clarified from what is currently in the protocol to only include participants who met Inclusion/Exclusion criteria. If a participant was randomised in error after not meeting inclusion/exclusion criteria, then they would not be included in this population.
- The primary endpoint multiple imputation sensitivity analysis was changed to be performed using the CMH test initially prescribed to test the endpoint instead of the nonparametric, randomisation-based ANCOVA as the nonparametric ANCOVA is supplemental to the primary endpoint.
- Analytic approach has been changed for Secondary endpoint 6: Participants' percentage of visits with opioid abstinence (defined as negative UDS and TLFB for opioid use) overall (Weeks 2 to 38 inclusive). The protocol specifies the analysis to the be same as for the "primary endpoint," however, the CMH test cannot be performed for a continuous outcome, so only the nonparametric randomisation based ANCOVA will be performed.

6.3 Schedules of Events

The Schedules of Events can be found in the protocol.

6.4 Methods to Manage Missing Data

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

The missing value handling approach for the primary efficacy endpoint is described in Section 5.3.1.1.1. Other strategies include considering all missing TLFB outcomes as positive and only considering missing opioid outcomes as positive if a participant discontinued due to lack of efficacy or an adverse event specifically as prescribed by the analysis. No imputation of missing values will be performed for safety [redacted].

Details for specific additional missing data handling approach(es) are provided below.

6.4.1 Derivation of Overall UDS Result for Opioids Use

Results of on-site dipstick UDS and centrally tested UDS will be used for primary, secondary, and exploratory efficacy endpoint analyses described in this SAP. A urine dipstick is performed onsite at Screening, Week 1 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, or the result is not available for a scheduled visit, the on-site dipstick UDS, if available for that visit, will be used.

6.4.1.1 Centrally Tested UDS

Centrally tested UDS, including referral lab testing for quantification results, provides individual results (negative, positive, or quantified) for each of the different opioid drugs being tested. The overall opioid UDS result will be derived as follows:

1-UDS fentanyl test result will be derived as follows for each visit

a. Check for a Fentanyl urine screen result: if positive or missing, proceed to step b. If negative, report Fentanyl result as “Negative.” (Fentanyl Screen Urine test code: UFENTSCNMS and FNTUSCREEN)

b. Check for quantification lab test result. If a quantification lab test result exists, the quantification result specific for Fentanyl (excluding Nor-fentanyl) will be used. ‘Not detected’ or ‘<1.0 ng/ml’ will be assigned as “Negative”, other values will be assigned as “Positive.” Fentanyl specific quantification lab codes include: UFENTCNNMS, UFENTCNMS1, FNTUQUANT).

c. If no quantification result exists, the urine screen result should be used.

2-Overal UDS opioid result will be based on the tests for opiates, methadone, and fentanyl (derivation described in 1):

a) “Opioid Positive” if at least 1 individual test result is positive.
b) “Opioid Negative” if all 3 test results are negative.
c) “Opioid Missing” for other scenarios, e.g., if all 3 test results are missing, or if one test result is missing and the other 2 test results are either negative or missing.

6.4.1.2 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.

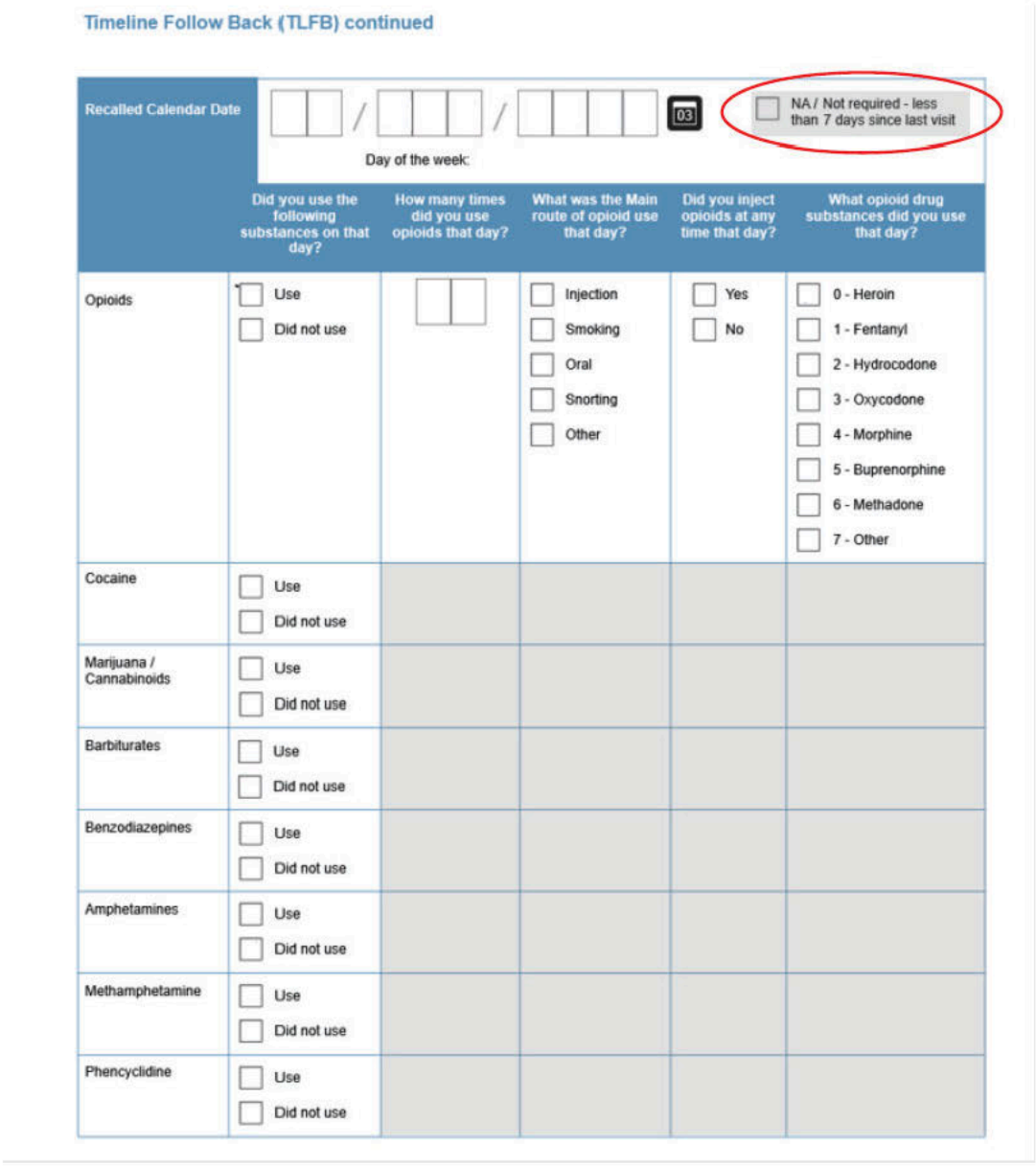
The algorithm to determine the on-site dipstick overall UDS opioid result uses 4 test results (1 combined test result for opioids/morphine, and 3 individual test results for oxycodone, methadone, and fentanyl) as follows:

- "Opioid Positive" if at least 1 test result is positive.
- "Opioid Negative" if all 4 test results are negative.
- "Opioid Missing" for other scenarios, e.g., 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.

6.4.2 Imputation and Derivation of Daily TLFB Result for Opioids use

The TLFB asks participants to retrospectively estimate their daily drug use for each of the past 7 days prior to the visit. For each of the 7 days, the participant should report whether or not opioids were used for that day ("Use" or "Did not Use"). Additional questions for opioids use include "the number of times used that day", "main route of opioid use" if an injectable route was used, and if specific opioid drug/substance of interest was used. Figure 2 is a screen shot of the TLFB questions. Imputation and derivation of TLFB variables for a daily record will follow the rules in order as described in Table 17.

Figure 2. Timeline Follow Back (TLFB)



Timeline Follow Back (TLFB) continued

Recalled Calendar Date ☐☐ / ☐☐☐ / ☐☐☐☐ 03 ☐ NA / Not required - less than 7 days since last visit

Day of the week:

	Did you use the following substances on that day?	How many times did you use opioids that day?	What was the Main route of opioid use that day?	Did you inject opioids at any time that day?	What opioid drug substances did you use that day?
Opioids	☐ Use ☐ Did not use	☐☐	☐ Injection ☐ Smoking ☐ Oral ☐ Snorting ☐ Other	☐ Yes ☐ No	☐ 0 - Heroin ☐ 1 - Fentanyl ☐ 2 - Hydrocodone ☐ 3 - Oxycodone ☐ 4 - Morphine ☐ 5 - Buprenorphine ☐ 6 - Methadone ☐ 7 - Other
Cocaine	☐ Use ☐ Did not use				
Marijuana / Cannabinoids	☐ Use ☐ Did not use				
Barbiturates	☐ Use ☐ Did not use				
Benzodiazepines	☐ Use ☐ Did not use				
Amphetamines	☐ Use ☐ Did not use				
Methamphetamine	☐ Use ☐ Did not use				
Phencyclidine	☐ Use ☐ Did not use				

Table 17. Imputation/Derivation on Opioids Use Variables for Daily TLFB Result

TLFB Variable (question) for Imputation	Condition for Imputation	Imputation Rule
Overall Opioid Use (Did you use opioids on that day?) [1]	Overall Opioid Use is missing, and • reported number of times of opioid use >0, or • reported nonmissing main route of opioid use, or • reported injecting opioid, or • reported specific opioids drug substance	Impute Opioids="Use"
Times of Opioids use (How many times did you use opioids on that day?)[2]	Times of opioids use missing, and Opioids="Did not use"	Impute Times of Opioids use=0
Opioids Injection (Did you inject opioids at any time that day? Yes/No))	Opioid injection is missing, and Opioids="Did not use"	Impute Opioid Injection="No"
	Opioid injection is missing, and reported main route="Injection"	Impute Injection="Yes"

[1]If participant reported Opioids Use="Did not use", but reported times of opioid use >0, or reported nonmissing main route of opioid use, or reported injection, or reported opioids drug/substance, then opioids may be derived="Use".

TLFB administration date will determine when TLFB results align with a visit, including determination of Baseline values. If a participant reports duplicate TLFB entries, the date of the earliest administration will be used. Induction TLFB results do not need to be reported in the ADaM datasets, however, should be included in an SDTM domain. In SDTM, the administration date should be the primary tagged visit date for each TLFB entry with the recall date added as additional identifier variable. If multiple TLFB results exist prior to the Week 1 Day 1 dose, the entry with the most recent administration date that aligns with the date of first injection should be assigned as the Week 1 Day 1 result. If the same administration date exists for multiple nominal visits, the nominal visit should be used. TLFB Baseline will be derived separately from Analysis Visit values due to the potential for overlapping recall days across multiple records.

6.4.3 Multiple Imputation for the Primary Endpoint Sensitivity Analysis

The following SAS code will be used to generate a minimum 50 datasets with multiply imputed opioid use outcomes (Negative or Positive) separately for each DB treatment arm:

```
PROC MI data=MIIN out=MIOUT nimpute=50 seed=123456;
  Class OPI: Cov1 - CovX;
  Var Cov1 - CovX OPI:;
  Monotone logistic(OPI20) logistic(OPI22) logistic(OPI24)
logistic(OPI26) logistic(OPI30) logistic(OPI34);
```

```
run;
```

The var statement determines the variables that contribute towards the imputation in the order that they are listed, preferably in order of least missing to most missing. The Monotone logistic statement specifies the variables to be imputed with logistic regression and specifies a monotone missing pattern. All risk factors listed in Section 5.1.6 will be included as contributing covariates towards the imputation (age & BMI will only be included on a continuous basis). Continuous variables do not need to be listed in the class statement.

After calculating overall percentage of abstinence as well as the response variable of 80% abstinence across Weeks 20 to 38 (Yes/No) for each participant in each imputation, the following SAS code will be used analyse each of the 50 imputation result datasets. The CMH statistic will be standardized using the square root transformation for each imputation.

```
*** Perform CMH test;
proc freq data=miout;
tables Stratum1*Stratum2*TRTGRP*Response / CMH riskdiff sparse;
output out=stats cmh riskdiff;
by _IMPUTATION_;
run;
```

Note: Separate calculation may be needed to produce counts for the CMH adjusted risk difference calculation using the Sato (1989) variance formula.

```
*** Apply Square Root transformation to the CMH statistic and
 standardize the resulting normal variable;
DATA cmh; SET stats;
where Stratum1=' ' and Stratum2=' ';
 cmh_value= sqrt(_CMHGA);
 cmh_sterr = 1.0;
RUN;
```

The following SAS code will be used to combine the 50 imputation results datasets post-analysis to produce pooled estimates of the adjusted risk difference and CMH statistic. 95%CIs and the CMH statistic p-value will be produced from the pooled statistics.

```
*** Combine results - CMH Weighted Difference;
PROC MIANALYZE DATA=stats;
 ODS OUTPUT PARAMETERESTIMATES=parm_dcmh;
 MODELEFFECTS dcmh;
 STDERR dcmh_se;
RUN;
*Scale to percent;
data dcmh; set parm_dcmh;
Diff=estimate*100;
Lower=lclmean*100;
Upper=uclmean*100
run;
*** Combine results - CMH Statistic;
PROC MIANALYZE DATA=cmh;
 ODS OUTPUT PARAMETERESTIMATES=parm_cmh;
 MODELEFFECTS cmh_value;
 STDERR cmh_sterr;
RUN;
```

Details may be found in the official SAS documentation for the MI and MIANALYZE procedures. Code may be adjusted as necessary for accurate analyses.

https://support.sas.com/documentation/onlinedoc/stat/141/mi.pdf

http://support.sas.com/documentation/onlinedoc/stat/143/mianalyze.pdf

6.4.4 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 DB maintenance 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.

For partial AE start date, if missing day and month, it will be handled as below:

- 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.

For partial AE start date, if missing month only, the day will be treated as missing and both month and day will be replaced according to the above procedure.

For partial AE start date, if missing day only, it will be handled as below:

- 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.

6.4.5 Missing Time Information for Adverse Events

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

6.4.6 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.

For partial medication start date, if missing day and month, it will be handled as below:

- 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.

For partial medication start date, if missing month only, the day will be treated as missing and both month and day will be replaced according to the above procedure.

For partial medication start date, if missing day only, it will be handled as below:

- 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.

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.

For partial medication stop date, if missing day and month, it will be handled as below:

- 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.

For partial medication stop date, if missing month only, the day will be treated as missing and both month and day will be replaced according to the above procedure.

For partial medication stop date, if missing day only, it will be handled as below:

- 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.

6.4.7 Missing Time information for Concomitant Medications

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

6.5 Prior Medications and Concomitant Medications

The definitions for prior and concomitant medications for whole study treatment period are found in Table 18 Table 19. Definitions of Concomitant Medications (for OLTP) The definitions for concomitant medications for OLTP are found in Table 19 Table 20. The definitions for concomitant medications for DBTP are found in Table 20 If the time is missing, then only the date will be used. See Section 6.4 (appendix) for handling of missing date information.

Table 18. Definitions of Prior and Concomitant Medications (for whole study treatment period)

End Date/Time of Nonstudy Medication	Start Date/Time of Nonstudy Medication			
	Missing	<Start Date/time of Study Medication[a]	≥Start Date/time and <End Date/ time of Study Medication	≥End Date/ Time of Study Medication
Missing (includes flagged as "Ongoing")	Prior Concomitant	Prior Concomitant	Concomitant	Not a medication on study
<Start date/time of study medication	Prior	Prior	Data Error	Data Error
≥Start date/time and <end date/time of study medication	Prior Concomitant	Prior Concomitant	Concomitant	Data Error
≥End date/time of study medication	Prior Concomitant	Prior Concomitant	Concomitant	Not a medication on study

[a] Start date/time of study medication is the date/time of first dose of RBP-6000, end date/time of study medication is the date/time of the last administration of RBP-6000.

Table 19. Definitions of Concomitant Medications (for OLTP)

End Date/Time of Nonstudy Medication	Start Date/Time of Nonstudy Medication			
	Missing	<Start Date/time of Study Medication[a]	≥Start Date/time of Study Medication and <End Date/time of Study Medication	≥End Date/time of Study Medication
Missing (includes flagged as "Ongoing")	Concomitant	Concomitant	Concomitant	Not a medication in OLTP
≥Start date/time of study medication	Concomitant	Concomitant	Concomitant	Data error

a Start date/time of study medication is the date/time of first dose of RBP-6000, end date/time of study medication is the date/time of the last administration of RBP-6000 up through the first RBP-6000 maintenance dose (Injection 3), whichever is the last.

Table 20. Definitions of Concomitant Medications (for DBTP)

End Date/Time of Nonstudy Medication	Start Date/Time of Nonstudy Medication			
	Missing	**<Start Date/time of Study Medication[a]**	**≥Start Date/time of Study Medication and <End Date/time of Study Medication**	**≥End Date/time of Study Medication**
Missing (includes flagged as "Ongoing")	Concomitant	Concomitant	Concomitant	Not a medication on study
≥Start Date/time and <End Date/time of Study Medication	Concomitant	Concomitant	Concomitant	Data error
≥End Date/time of Study Medication	Concomitant	Concomitant	Concomitant	Not a medication on study

a Start date/time of study medication is the date/time of first RBP-6000 maintenance dose in DBTP (Injection 3), end date/time of study medication is the date/time of the last administration of RBP-6000 maintenance dose.

6.6 Customised MedDRA Queries

Table 21. 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
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

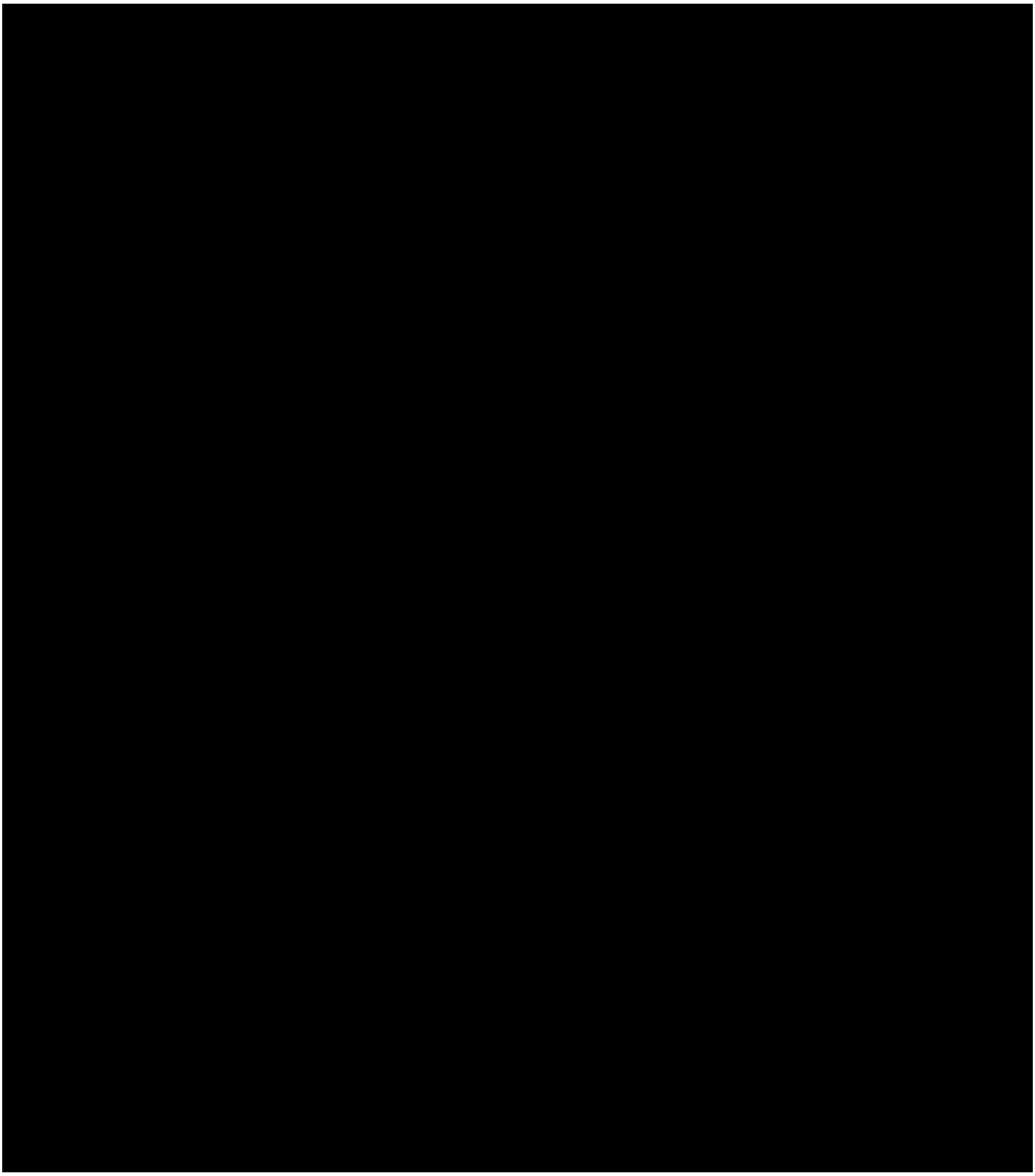
Hepatic steatosis	Anorectal varices haemorrhage
Hepatitis fulminant	Intrahepatic portal hepatic venous fistula
Hepatobiliary disease	Peritoneovenous shunt
Hepatocellular foamy cell syndrome	Portal shunt
Hepatocellular injury	Portal shunt procedure
Hepatopulmonary syndrome	Small-for-size liver syndrome
Hepatorenal failure	Spider naevus
Hepatorenal syndrome	Splenorenal shunt
Hepatotoxicity	Splenorenal shunt procedure
Intestinal varices	Spontaneous intrahepatic portosystemic venous shunt
Intestinal varices haemorrhage	Stomal varices
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
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

Table 22. 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
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 Summary of Efficacy Endpoints

Table 23. Summary of Efficacy Endpoints

Endpoint	Outcome assessment	Measure	Time Period
Primary	UDS & TLFB	Proportion of responders (negative results ≥80%)	Weeks 20 to 38
Secondary 1	TLFB	Percentage days used	Weeks 10 to 38
Secondary 2	UDS & TLFB	Proportion of responders (negative results ≥80%)	Weeks 10 to 38
Secondary 3	UDS & TLFB	Percentage visits abstinent	Weeks 10 to 38
Secondary 4	UDS & TLFB	Proportion of responders (negative results ≥80%)	Weeks 30 to 38
Secondary 5	TLFB	Proportion of responders (negative results ≥80%)	Last 5 visits
Secondary 6	UDS & TLFB	Percentage visits abstinent	Weeks 2 to 38
Secondary 7	TLFB	Percentage days used	Weeks 2 to 38
Secondary 8	TLFB	Percentage days used via injection	Weeks 10 to 38
Secondary 9	TLFB Number of Times Used	Average times used per week	By visit (TLFB week)
Secondary 10	TLFB Number of Times Used	Average change from Screening Baseline	By visit (TLFB week)
Secondary 11	UDS & TLFB	Proportion abstinent	By visit
Secondary 12	TLFB	Average number of days used	By visit
Secondary 13	Study Discontinuation/ Completion	Time on treatment	Week 6 to EOT
Secondary 14	Exposure	Proportion who completes final injection	Week 34

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