Study Title An Open-Label, Long-Term Safety and Tolerability Study of Depot Buprenorphine (RBP-6000) in Treatment-Seeking Subjects With Opioid Use Disorder

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Statistical Analysis Plan

Sponsor:	Indivior Inc.
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Approvals

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1.0 Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the final reporting and analyses of data collected for the full study (Protocol RB-US-13-0003).

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol dated 04AUG2016 and CRF dated 22SEP2016.

The SAP for study RB-US-13-0003 was developed in three stages. SAP Version 1.0was finalized so thatprogramming could begin earlier in the process. SAP Version 2.0 was finalized before the interim database lock and was used for the interim anlaysis. This SAP version 3.0 will be finlaised and used for the final reporting and analysis of the full study data.

1.1 Changes from Protocol

The following changes to the analysis planned in the protocol were made:

- The addition of an analysis set (Run-In Safety Analysis Set) was made to aid in the analysis of the Run-In period.
- Electrocardiograms (ECGs) overall impression summaries will only be summarized by normal or abnormal; protocol says they should be summarized by normal, abnormal not clinically significant, or abnormal clinically significant, but there is no distinction of clinical significance for abnormal results.
- There will be no mixed-effect model for repeated measure analysis on the clinical outcome data, Clinical Opiate Withdrawal Scale (COWS), Subjective Opidate Withdrawal Scale (SOWS), and Opioid Craving Visual Analog Scale (VAS), due to the nature of the study design.
- The Clinical Outcome Assessment Analysis Set has been removed since this is a safety study.
- Total score for electronic Columbia Suicide Severity Rating Scale will not be summarized.
- Physical examination data is collected as a part of the corresponding safety assessment (i.e. adverse events (AEs), vital signs).

2.0 Study Objectives

Indivior Inc., formerly Reckitt Benckiser Pharmaceuticals Inc. (RBP) is developing RBP-6000, a long-acting formulation of buprenorphine for monthly subcutaneous (SC) injection, for the treatment of opioid use disorder (OUD).

2.1 Primary Objective

To assess the long-term safety and tolerability of RBP-6000 SC injections in subjects with opioid use disorder.

2.2 Secondary Objectives

To collect clinical outcome data with RBP-6000 SC injections in subjects with opioid use disorder.

2.3 Tertiary Objectives

To evaluate the:

- Pharmacokinetics (PK) of RBP-6000,
- Relationship between RBP-6000 PK and clinical outcome data, and
- Impact of RBP-6000 on health and economic outcomes.

A stand-alone SAP will be developed for the health and economic outcomes. PK will be reported separately from the clinical study report.

3.0 Study Design

This is a multicenter, open-label, long-term Phase III safety study in which approximately 600 subjects diagnosed with opioid use disorder will be enrolled (approximately 300 subjects who did not participate in the RB-US-13-0001 study [hereafter referred to as "*de novo*" subjects] and approximately 300 subjects that completed the RB-US-13-0001 study [hereafter referred to as "roll-over subjects")]. Subject participation will be based on the Investigator's determination that initiation or continuation of study treatment is appropriate; and, that among subjects who are continuing from the RB-US-13-0001 study, there have been no significant protocol deviations or clinically important AEs that would preclude inclusion of the subject in RB-US-13-0003.

Before receiving the first injection of RBP-6000 in this safety study, all subjects will undergo a Run-In period with SUBOXONE® (buprenorphine/naloxone) sublingual film to avoid precipitating a withdrawal syndrome and to preserve blind in subjects treated with placebo in the RB-US-13-0001 study. Subjects will be inducted onto SUBOXONE sublingual film consistent with the SUBOXONE sublingual film label; they will then complete a 1 to 11 day SUBOXONE sublingual film Dose Adjustment period.

Once subjects meet the criteria (on Day -11 to Day -1) of no significant opioid craving (≤20 mm on the Opioid Craving VAS and no significant withdrawal (≤12 on the COWS) they may receive the first SC injection of RBP-6000 (containing 300 mg of buprenorphine). Subjects with significant withdrawal signs/symptoms (defined as > 12 on the COWS) or significant cravings for opioids (defined as >20 mm on the Opioid Craving VAS) after the end of the 2-week SUBOXONE sublingual film Run-In period will not be eligible to continue in the study and will be referred for treatment.

On Day 1 of the study (initiation of study drug injections), all subjects will receive a SC injection of 300 mg of buprenorphine in RBP-6000. Subsequent doses of RBP-6000 may be adjusted down to 100 mg and back up to 300 mg based on the medical judgment of the Investigator. After injection of RBP-6000, subjects will not be permitted to receive supplemental SUBOXONE sublingual film during the RBP-6000 treatment period. Subjects who require supplemental SUBOXONE sublingual film or other sublingual buprenorphine pharmacotherapy during the RBP-6000 treatment period will be withdrawn from the study and referred for appropriate treatment.
Subjects will return to the clinic for monthly injection visits (every 28 -2/+4 days) for a total of up to 12 injections for *de novo* subjects or for a total of 6 injections for roll-over subjects. ECG recordings and vital signs will be collected pre and post each SC injection. All ECGs will be interpreted by a central monitoring facility. Subject-reported injection site pain VAS scores will be collected at various times up to 1 hour after each injection. Local injection site grading will be collected at various time points starting immediately after injection and will be evaluated for pain, tenderness, warmth, itching, erythema, inflammation or swelling, and bruising using a 4-point severity scale. At each visit after injections begin, the injection site will be assessed by site staff and will also be evaluated for evidence of attempts to remove the depot.
Subjects will need to return to the clinic weekly for the first 5 weeks and biweekly (i.e., every 2 weeks) until injection 6, and monthly for the rest of the study period for urine drug screens (UDS), Timeline Followback (TLFB) interviews, opioid craving VAS evaluation, COWS and subject reported outcomes (SOWS). Subjects will continue to receive counseling (manual-guided behavioral therapy) during the study. Safety assessments will be collected at each injection visit and/or at injection follow-up visits and will include the following: vital signs, electronic Columbia Suicide Severity Rating Scale (eC-SSRS) responses, ECGs, laboratory tests (hematology, chemistry, urinalysis, and pregnancy test), concomitant medications, and AEs.

Approximately 2 months prior to the scheduled end of study (EOS) visit, the subject's ongoing treatment options will be reviewed with the investigator. At the EOS, 2 transition treatment options may be offered if the subject is eligible:

- Subjects who complete RBP-6000 treatment period may be offered entry into an open label extension study of RBP-6000 (Study INDV-6000-301). Eligibility will be based on meeting the inclusion and exclusion criteria and the medical judgment of the Investigator.
- Subjects who do not meet the eligibility criteria of the extension study, or subjects who do not wish to enroll may alternatively enter a 4-week SUBOXONE transition period if deemed suitable by the investigator. Subjects should be dosed using the Investigators medical judgment. Any additional unscheduled visits required by the subject for the SUBOXONE transition will not be compensated by the Sponsor.

Subjects that did not enroll onto the INDV-6000-301 should be contacted by telephone approximately 4 weeks after EOS for a safety follow-up assessment of AEs and use of concomitant medications.
The safety assessments used include evaluations of AEs, serious AEs (SAEs), discontinuations from study due to AEs; local injection site tolerability (e.g., injection site grading); injection site pain using a subject-reported VAS; suicidality using the eC-SSRS, concomitant medications; changes in clinical laboratory results; vital sign measurements; 12-lead ECGs, and physical examination results.
The instruments used to measure clinical outcomes (e.g., COWS, SOWS, Opioid Craving VAS, and eC-SSRS) were developed to measure the specific symptoms exhibited by and the challenges facing opioid-dependent individuals.

3.1 Sample Size Considerations

This study is designed to assess the long-term safety, tolerability, and clinical outcomes of RBP-6000 SC injections in subjects with opioid use disorder. Approximately 300 *de novo* subjects as well as approximately 300 roll-over subjects who completed the RB-US-13-0001 study will be enrolled into this long-term safety study. The planned number of subjects was designed to ensure at least 100 subjects reach 1 year of treatment with RBP-6000 (as advised in the ICH-E1A Guideline – The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions).

3.2 Randomization

This is an open-label study and does not involve randomization.

3.3 Study Duration

The expected maximum duration of participation for *de novo* subjects is up to approximately 55 weeks consisting of up to a 7-day screening period, up to a 14-day SUBOXONE sublingual film Run-In, up to a 48-week open-label treatment period, and a 4-week follow-up and transition period when subjects will receive the same dose of SUBOXONE that they received at Day -1 and their ongoing treatment options will be reviewed.
The expected maximum duration of participation for roll-over subjects is up to approximately 31 weeks, consisting of up to a 7-day screening period, up to a 14-day SUBOXONE sublingual film Run-In, a 24-week open-label treatment period, and a 4-week follow-up and transition period when they will receive the same dose of SUBOXONE that they received at Day -1 and their ongoing treatment options will be reviewed.
If at least 100 subjects reach 1 year of exposure to RBP-6000 in RB-US-13-0001 and RB-US-13-0003, the study may be stopped early, and all remaining subjects will complete EOS procedures and enter the SUBOXONE Transition Period/Safety Follow-up.
Subjects who receive at least 1 dose of RBP-6000 and discontinue the trial for any reason will be required to complete the Early Termination (ET) visit.

4.0 Study Variables and Covariates

4.1 Primary Variables

The following variables will be evaluated to assess the safety and tolerability of RBP-6000:

- Incidence of treatment-emergent adverse events (TEAEs).
- Changes in clinical laboratory results.
- Vital sign measurements.
- Other variables related to safety
    - 12-lead ECGs.
    - Medical history.
    - Suicidality using the eC-SSRS.
    - Prior and concomitant medications.
    - Local injection site tolerability (e.g., injection site grading).
    - Injection site pain using a subject-reported VAS.
    - Physical examination results.

4.2 Secondary Variables

The following secondary variables will be evaluated to analyze clinical outcomes:

- COWS total score.
- SOWS total score.
- Opioid Craving VAS total score.
- Self-reported illicit drug use.
- Percentage of negative urine drug screen samples.

4.3 Tertiary Variables

- PK of RBP-6000.
- Health economic and outcome data (to be analyzed in a separate SAP)
    - Beck Depression Inventory.
    - Brief Pain Inventory.
    - EuroQoL EQ-5D-5L.
    - 36-Item Short Form Health Survey.
    - Medication Satisfaction Questionnaire.
    - Healthcare Resource Utilization.
    - Treatment Effectiveness Assessment.
    - Addiction Severity Index Lite.

5.0 Definitions

Abstinent

A subject is defined as being abstinent from opdioid drug use if his/her UDS and TLFB results for opioids are negative.

Age

Age is defined as date of informed consent – date of birth + 1.

Baseline and Change from Baseline

Baseline is defined as the last non-missing value prior to SC injection of RBP-6000 on Day 1 of the RB-US-13-0003 study.
Change from baseline = (post-baseline value – baseline value).

Completed Study
A subject will be deemed to have completed the study if he/she has received 6 doses (roll-over) or 12 doses (de-novo) of RBP-6000 and completed the EOS visit.

Clinical Opioid Withdrawal Scale Total Score
The COWS total score is defined as the sum of the responses to the 11 questions including resting pulse rate, gastrointestinal upset, sweating, tremor, restlessness, yawning, pupil size, anxiety or irritability, bone or join aches, gooseflesh skin, and runny rose or tearing. Each answer to a corresponding question is assigned a value between 0 and 5. If 2 or more answers are missing, then a total score will be set to missing. If 1 question is missing, then the total score will be defined as the average of the non-missing responses multiplied by the total number of answered questions (hereafter referred to as normalized).

Prior and Concomitant Medications

Prior medications will be any medication taken before the date of first dose of SUBOXONE (during run-in) in the RB-US-13-0003 study.

Concomitant medications will be defined as any medication taken on or after the first dose of SUBOXONE (during run-in) in the RB-US-13-0003 study.

Concomitant medications include those medications that are ongoing at the time a subject rolls-over from the RB-US-13-0001 study. Medications or supplements that meet any of the following criteria will be considered concomitant:

- Missing both start and stop dates
- Having a start date prior to the start of first dose of SUBOXONE and missing the stop date
- Having a stop date after the first injection missing the start date.

Subject Type

Subjects will be categorized as either de novo or roll-over (from the RB-US-13-0001 study.

Treatment-emergent Adverse Events
TEAEs are those that started following the first dose of RBP-6000 in this study or were present prior to the first dose of RBP-6000 in this study regardless of causality and increased in severity following administration of RBP-6000 regardless of causality≤30 days after the last dose of RBP-6000. All AEs which change in severity or relationship to RBP-6000 are assigned a new start date and captured as a new AE. AEs include those events that are ongoing at the time a subject rolls-over from the RB-US-13-0001 but these events will not be considered treatment-emergent.

Run-In Adverse Events
An AE for the run-in period is an AE that either commenced during the run-in period or was present prior to the initiation of run-in, but increased in severity during run-in, regardless of causality, and prior to the first injection of RBP-6000.

Outcome of Death
Any AE with an outcome of fatal or study discontinuation due to death.

Subjective Opioid Withdrawal Scale Total Score
The SOWS total score is defined as the sum of the responses to the 16 questions as indicated by the subjects on how they feel at the time of completed the questionnaire including anxiousness, yawning, perspiring, teary eyed, runny nose, goosebumps, shaky, hot flushes, cold flushes, bones and muscle achiness, restlessness, nausea, vomiting, muscle twitching, stomach cramps, and feeling like using now. Each answer to a corresponding question is assigned a value between 0 and 4. If 3 or more responses are missing, then a total score will be set to missing. If less than 3 responses are missing, then the total score will be normalized.

Suicidal Ideation Scoring

The suicidal ideation score ranges from 0 to 5 and depends on the answers to the suicidal ideation portion of the eC-SSRS. The score is the maximum suicidal ideation category (in the following order: 1 = wish to be dead, 2 = Non-specific active suicidal thoughts, 3 = active suicidal ideation with any methods (not plan) without intent to act, 4 = active suicidal ideation with some intent to act, without specific plan, and 5 = active suicidal ideation with specific plan and intent) present at the assessment. If all answers to these questions are “No” then the suicidal ideation score is 0.

Suicidal Ideation Intensity Rating:

The suicidal ideation intensity rating is the sum of the five intensity item scores to create a total score (range 0 to 25). The five intensity items include frequency, duration, controllability, deterrents, and reason for ideation. Each item is scored from 0 to 5 with 5 representing the most severe intensity.

Suicidal Behavior Scoring

The suicidal ideation score ranges from 0 to 5 and depends on the answers to the suicidal behavior portion of the eC-SSRS. The score is the maximum suicidal ideation category (in the following order: 1 = preparatory acts or behavior, 2 = aborted attempt, 3 = interrupted attempt, 4 = actual attempt, and 5 if the subject has an AE with a preferred term of completed suicide. If all answers to these questions are “No” and the subject does not have an AE with a preferred term of completed suicide then the suicidal behavior score is 0.

Treatment Duration (weeks)

Treatment duration will be defined as (treatment stop date – treatment start date + 1)/7 where treatment stop date is defined as date of last RBP-6000 injection + 28 days.

Percentage of Urine Drug Screen and Self-Report Results

Subjects' self-reported illicit drug use from the TLFB and results from the UDS will be combined into a single endpoint in the following manner:

- If both the TLFB and the UDS have a negative result at a particular visit, then the visit will be considered to have a negative result at that visit.
- If either the TLFB or UDS, or both, have a non-negative result at a particular visit, then the visit will be considered to have a non-negative result at that visit.
- To be conservative, missing UDS or TLFB data will be imputed as non-negative.

Urine Drug Screen Result for Opioids	Self-Report of Illicit Opioid Use Result	Overall Result
Nonnegative	Nonnegative	Nonnegative
Nonnegative	Negative	Nonnegative
Negative	Nonnegative	Nonnegative
Negative	Negative	Negative

Treatment Success

A subject is defined as a treatment success if ≥80% urine samples negative combined with self-reports negative.

Visit Window for Remapping of Early Termination visit

Duration will be derived in days as (ET visit date – treatment start date) + 1.

Visit window for safety and efficacy assessments.

Study Visit	Lower Window for Analysis Day (ADY)	Upper Window for ADY
Week 1 Day 1	1	1
Week 1 Day 2	2	5
Week 2 Day 8	6	12
Week 3 Day 15	13	19
Week 4 Day 22	20	26
Week 5 Day 29	27	38
Week 7 Day 43	39	54
Week 9 Day 57	55	68
Week 11 Day 71	69	82
Week 13 Day 85	83	94
Week 15 Day 99	95	110
Week 17 Day 113	111	122
Week 19 Day 127	123	138
Week 21 Day 141	139	166
Week 25 Day 169	167	194
Week 29 Day 197	195	222
Week 33 Day 225	223	250
Week 37 Day 253	251	278
Week 41 Day 281	279	306
Week 45 Day 309	307	335

If an ET visit/assessment happens any time between Day 1 and prior to End of Study visit, the following approach (Table) should be adopted to remap those ET visit to applicable study visit week based on the ADY variable value, defined as date of assessment – date of first dose + 1, of the ET date variable.

If Lower Window <= ADY (of ET date) <= Upper window, then set appropriate AVISIT value based on the above CRF study visits.

After re-mapping the ET visits to any of study visit weeks, if there are multiple records falling within the same week window, latest one with non-missing result will be flagged in analysis datasets and considered for analysis of by visit summary tables and figures.

6.0 Analysis Sets

6.1 All Screened Subjects

All screened subjects include any subject who signed the informed consent form.

6.2 Run-In Safety Analysis Set

The Run-In Safety Analysis Set will include all subjects who received at least 1 dose of SUBOXONE during the Run-In period of the study.

6.3 Safety Analysis Set

The Safety Analysis Set comprises all subjects who received at least 1 dose of RBP-6000 during the open-label treatment period of the study. This analysis set will be used for all safety analyses.

6.4 PK Analysis Set

The PK Analysis Set will include any subject who receives a dose of RBP-6000 or at least 1 dose of SUBOXONE sublingual film and has at least 1 PK sample collected post-dose.

7.0 Interim Analyses (Data Cut Review)

An interim safety analysis was conducted using all data up to and including the 12th August 2016. The data was anlysed and reported as per SAP version 2.0.

8.0 Data Review

8.1 Data Handling and Transfer

All of the data will come from the PRA Health Sciences data management group in SAS® dataset format (SAS version 9.4 or later) converted to Study Data Tabulation Model (SDTM) using SDTM Implementation Guide (SDTMIG) Version 3.1.3. Please refer to the Data Quality Plan for details.

The following vendors will be providing data for the study:

- WCT: PK data;
- ACM: Central laboratory data;
- ERT: SOWS, COWS, Opioid Craving VAS, Injection site grading scale, TLFB results, injection pain VAS, end time of the injections, and eC-SSRS data;
- Cardiocore: ECG data.

8.2 Data Screening

Beyond the data screening built into the Data Management Plan, the programming of analysis datasets, tables, figures, and listings (TFLs) provides additional data screening. Presumed data issues will be output into SAS logs identified by the word “Problem” and extracted from the logs by a SAS macro and sent to PRA Data Management.

Review of a pre-data cut subset TFL run allows for further data screening prior to lock. The pre-data cut subset TFLs will be discussed with the sponsor in a data review meeting to identify any final data issues and seek corrections prior to database lock for the interim lock and final lock. The PRA statistician and the sponsor must approve final database lock.

9.0 Statistical Methods

All statistical analyses will be performed using SAS® Version 9.4 or higher.

Categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place; except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts. When assessments are not applicable (ie Post injection 6 visits for roll-over subjects), an N/A will displayed instead of a zero,

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. The minimum, maximum, and 95% CI values (in some instances) will be displayed to the same level of precision as the raw data, the median and mean to one additional decimal place and the SD to two additional decimal places. The maximum number of decimal places will be 4. All summaries will be presented by subject type (de novo or roll-over) unless otherwise stated.

Unless otherwise stated, summaries will be presented by subject type (*de novo* or roll-over and total). Missing values will be presented by blank spaces. For partially missing dates, the information present will be printed; e.g., "--JAN2000".

For dichotomous outcome measures such as urine drug screen results (negative; non-negative) and self-reports for illicit opioid use (negative; non-negative), any missing observation will be set equal to "non-negative." Missing results for substances other than opioids will not be imputed. For all continuous endpoints (e.g., COWS, SOWS, and VAS), the missing data will not be imputed.

Only scheduled assessments per protocol Amendment 4 will be presented in tables and figures except for worst case post-baseline and at any time types of analyses (all post-baseline including unscheduled assessments data will be considered for this derivation) but all data will be presented in the listings.

9.1 Subject Disposition

The number and percentage of all screened subjects in each analysis set will be summarized (de-novo, roll-over and total).

A summary of the number and percentage of all screen and enrolled subjects (de-novo, roll-over, total) at each center will be presented, including those centers who screened or enrolled no subjects.

The number and percentage of subjects screened, screen failures, entered the Run-In period, Run-In failures (including those who prematurely discontinued during the Run-In period), entered the RBP-6000 treatment period (i.e. received at least 1 dose of RBP-6000), and who completed the study will be presented, together with the number and percentage of subjects who prematurely discontinued from the RBP-6000 treatment period or in the Run-In period prematurely and a breakdown of the corresponding reasons for study discontinuation separately in each period.

A listing of all subjects' analysis set inclusions, disposition, and reasons for study discontinuation will be presented.

A listing of the inclusion/exclusion reasons for screen failure will be provided.

9.2 Protocol Deviations

A listing of subjects in the Safety Analysis Set with important protocol deviations (PDV) will be provided. An important deviation is defined as:

- Subject consent was never obtained
- Inclusion/Exclusion/Enrollment Criteria were violated

9.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics (sex, ethnicity, race, age [years and categories of ≥18-<30, ≥30-<45, ≥45-<60, ≥60, and ≥65], weight [kg], height[cm], waist-to-hip ratio, body mass index [BMI; kg/m^2], tobacco use [never, former, current], caffeine use [never, former, current], alcohol use [never, former, current]) will be summarized by subject type (de novo, roll-over and total) using descriptive statistics for subjects in the Safety Analysis Set. Qualitative variables (sex, ethnicity, race, age categories, tobacco use, caffeine use, alcohol use) will be summarized using frequencies while quantitative variables (age, weight, height, BMI, waist-to-hip ratio) will be summarized using mean, SD, median, minimum, and maximum. Demographic and baseline data will also be listed for all screened subjects.

A further summary of the subjects will be presented for subgroups including opioid users at screening [injectable vs. non-injectable] and use of opioids during the Run-In period as indicated by a nonnegative UDS in the Safety Analysis Set.

History of drug use will be presented by substance and previous use for subjects in the Run-In Safety Analysis Set. All drug use history collected on the CRF will be listed including days of opioid drug use in the past 30 days, years of regular drug use in lifetime, and route the substance was administered for all screened subjects.

9.3.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 and summarized by the number and percentage of subjects in each system organ class (SOC), preferred term (PT), and subject type in the Safety Analysis Set.

Listings of medical history events for subjects in the Run-In Safety Analysis Set will be provided.

9.3.2 Prior and Concomitant Medications

Medications received prior to exposure to SUBOXONE, categorized by preferred name and ATC level 4 class according to World Health Organization Drug Dictionary (WHODRUG; Version 2014SEP01DDE), will be summarized for the Safety Analysis Set. The number and percentage of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication. Additionally, medications received concomitantly with study will be summarized in the same manner for the Safety Analysis Set.

All prior and concomitant medications will be presented in separate listings for the Safety Analysis Set.

9.4 Study Treatment Exposure

A summary of the exposure to SUBOXONE during the Run-In period will be summarized by Run-In period (induction/dose adjustment), visit, administration/dispensation, and dosage for the Run-In Safety Analysis Set. A listing of SUBOXONE exposure (administration/dispensation) will be provided.

Exposure will be derived as date of first RBP-6000 injection on the RB-US-13-0003 study, to 28 days after the last RBP-6000 injection on this study.

The duration of exposure in the 0-<4 weeks through 48 – <52 weeks, total number of RBP-6000 doses received, the total number of actual doses as a continuous summary, and the total number of actual doses as a categorical summary will be presented for the Safety Analysis Set. RBP-6000 exposure data will also be listed detailing the dose of RBP-6000 received at each injection and the number of days between injections.

The number of subjects who have early removal of the RBP-6000 depot by physician will be presented for the Safety Analysis Set. Early removal of the study drug depot data including the reason and removal date and time will be listed.

9.5 Efficacy Analysis

All efficacy endpoints will be summarized for the Safety Analysis Set.

9.5.1 Self-reported and Urine Samples Illicit Drug Use

Urine Drug Screen Result

A subject will be deemed to have a 'non-negative' result for opioids when his/her urine drug screen result is greater than the upper limit of normal for any of the opioid drugs tested (Section 9.6.2.4).

Opioid Drug Classification (UDS)

Drug	Opioid?
Amphetamine	No
Barbiturates	No
Benzodiazepine	No
Benzoylecgonine	No
Buprenorphine[1]	No
Cannabinoids	No
Codeine	Yes
Hydrocodone	Yes
Hydromorphone	Yes
Methadone	Yes
Morphine	Yes
Opiate	Yes
Oxycodone	Yes
Oxymorphone	Yes
Phencyclidine	No

[1] Buprenorphine urine testing for de novo subjects was only included during the screening period; and urine testing for buprenorphine during the screening period was subsequently removed from the protocol per protocol amendment #1. The only subjects who tested positive during screening (when RBP-6000 was not being administered) were de novo subjects. Roll-over subjects were not tested for buprenorphine during screening. Neither de novo nor roll-over subjects were tested for buprenorphine at baseline or post-RBP-6000 administration.

Opioid Drug Classification (TLFB)

Drug	Opioid?
Amphetamine/Methadone[1]	Yes
Barbiturates	No
Benzodiazepine	No
Buprenorphine	Yes
Cocaine	No
Ethanol	No
Methadone	Yes
Opioids	Yes
PCP	No

[1] The TLFB interview called for an assessment of the use of amphetamine/methamphetamine. However, the ePRO tablet was programmed to ask for the use of amphetamine/methadone. As a result, the primary analysis for the TLFB question of amphetamine/methadone will be assumed to be non-negative. A sensitivity analysis will be performed where the answer to the TLFB question of amphetamine/methadone of 'Use" will be assumed to be negative.

Subjects' self-reported illicit drug use from the TLFB and opioid detection from the UDS will be summarized together by showing the number and percentage of subjects who have ≥0, ≥10%, ≥20%, ≥30%, ≥40%, ≥50%, ≥60%, ≥70%, ≥80%, ≥90%, ≥100% negative result and a continuous summary of the percent negative. The cumulative distribution function (CDF) of the percentage abstinence (negative self-reports from the TLFB combined with negative UDS for opioid use) will be presented in a graph. The graph will present the proportion of subjects who remained at least a given percentage abstinent from opioid drug

use, as defined in Section 5; for example, 10% on the x-axis represents the proportion of subjects who had at least 10% of their self-reported opioid drug use combined with UDS as abstinent.

Additionally, a table showing the percentage of subjects with negative results at each visit will be provided.

All missing results for opioids were considered nonnegative for opioids. Opioids non-negative indicates detection of buprenorphine (only self-reports), codeine, hydrocodone, hydromorphone, methadone, morphine, opiates, oxycodone, and oxymorphone in the urine drug screen and reporting of amphetamine/methadone, buprenorphine, methadone, and opioids use in the timeline followback.

The number and percentage of subjects abstinent between visits will be summarized by subject type for the Safety Analysis Set. Additionally, the time to first urine sample non-negative or TLFB self-report of non-negative for opioids will be analyzed in the Safety Analysis Set for subjects who are Abstinent on Day 1 using Kaplan-Meier analysis methods to determine the first quartile (25%) and median (days) along with their corresponding confidence intervals in each subject type and overall. Subjects who are abstinent throughout the trial will be censored on the date of their last negative urine sample of TLFB self-report for opioids.

The number and percentage of subjects who have a non-negative result in each substance tested in the UDS will be reported by subject type in the Safety Analysis Set. Additionally, the number and percentage of subjects at each visit who tested non-negative for non-opioid substances will be summarized by subject type in the Safety Analysis Set in a tables and in figures for amphetamine, barbiturates, benzodiazepine, cannabinoids, and phencyclidine.

Opioid TLFB and UDS results will be listed together. Additionally, all drugs identified in the TLFB interviews and detected in the UDS will be listed separately for the Safety Analysis Set.

9.5.2 Clinical Opioid Withdrawal Scale (COWS) Total Score

COWS total scores will be summarized by clinical visit and subject type using descriptive statistics (mean, median, SD, minimum, and maximum), including change from baseline. A listing of the COWS assessment will be provided for the Safety Analysis Set. Additionally, separate listings for the actual values (individual responses and total scores) and the change from baseline in total COWS score will be presented for the Safety Analysis Set.

A figure for the COWS scores over time will be created for all subjects in the Safety Analysis Set. An additional table and figure will be created for the Safety Analysis Set excluding subjects using illicit opioids (either by UDS or TLFB) at any time during the study.

9.5.3 Subjective Opioid Withdrawal Scale (SOWS) Total Score

SOWS total scores will be summarized using descriptive statistics (mean, median, SD, minimum, and maximum), including change from baseline. A listing of the SOWS assessment will be provided for the Safety Analysis Set. Additionally, separate listings for the actual values (individual responses and total scores) and the change from baseline in total SOWS score will be presented for the Safety Analysis Set.

A figure for the SOWS scores over time will be created for all subjects in the Safety Analysis Set. An additional table and figure will be created for the Safety Analysis Set excluding subjects using illicit opioids (either by UDS or TLFB) at any time during the study.

9.5.4 Opioid Craving VAS Total Score

Opioid Craving VAS total scores will be summarized using descriptive statistics (mean, median, SD, minimum, and maximum), including change from baseline for the Safety Analysis Set. Additionally, separate listings for the actual values and the change from baseline in opioid craving VAS total scores will be presented for the Safety Analysis Set.

A figure for the Opioid Craving VAS scores over time will be created for all subjects in the Safety Analysis Set. An additional table and figure will be created for the Safety Analysis Set excluding subjects using illicit opioids (either by UDS or TLFB) at any time during the study.

9.6 Primary Safety Analyses

9.6.1 Incidence of Adverse Events

9.6.1.1 Adverse Events

Imputation of AE (for determination of TEAE only) and concomitant medication start and stop dates:

Start Date: If only 'day' is missing, and the month and year are not the same as the month of first dose, then impute day with '01'. Otherwise, if the month and year are the same as the first dose date, use the first dose date. If 'day' and 'month' are missing, and 'year' is not missing, then impute month and day with month and day of the first dose date (assuming same 'year'). If 'day' and 'month' are missing and 'year' is not missing and is not the same year as first dose date, then impute with '01' for both 'day' and 'month'. If the start date is completely missing, it will be set to the first dose date.

Stop Date: If only 'day' is missing, impute day with last day of the month. If 'day' and 'month' are missing, and 'year' is not missing, then impute month with '12' and day with '31' (or date of study discontinuation/completion if earlier than 12-31 and year is the same as the year of discontinuation). If the stop date is completely missing, it will be set to the date of study discontinuation/completion. A stop date will not be applied to ongoing AEs or ongoing medications.

Treatment-related Adverse Events
Any AE with a relationship to study treatment of 'Related' or missing will be considered a treatment-related AE as determined by the Investigator.

A summary of treatment-emergent AEs will be presented for the Safety Analysis Set and the Run-In Safety Analysis Set, including the number of events reported, the number and percentage of subjects reporting at least one AE, the number and percentage of subjects with the following:

- Related AEs
- SAEs
- Related SAEs
- AEs with an outcome of death
- Severe TEAEs
- AEs leading to discontinuation

A breakdown of the number and percentage of subjects reporting each AE categorized by SOC and PT coded according to the MedDRA dictionary version 17.1 will be presented for the Run-In period using the Run-In Safety Analysis Set and for the open label RBP-6000 treatment period using the Safety Analysis Set. Note that counting will be by subject not event and subjects are only counted once within each SOC or PT. AEs/TEAEs related to SUBOXONE/study treatment will presented in a similar manner.

A further tabulation of events experienced by ≥5% of subjects by SOC and PT will be presented for the Safety Analysis Set.

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

Additionally, treatment-related AEs/TEAEs will be summarized by maximum severity (Mild, Moderate, or Severe). A breakdown of severe treatment-related AEs/TEAEs by SOC and PT will be provided.

All AEs (including non-TEAEs) recorded on the CRF will be listed.

9.6.1.2 Serious Adverse Events

SAEs and treatment-related SAEs will be summarized separately by SOC and PT for the Run-In Safety Analysis Set and the Safety Analysis Set.

All SAEs recorded on the CRF will be listed for all screened subjects.

9.6.1.3 Adverse Events Leading to Discontinuation

A summary of AEs/TEAEs and treatment-related AEs/TEAEs leading to discontinuation (defined as an event with an outcome of 'drug withdrawn' in the CRF) will be provided, grouped by SOC and PT, for the Run-In Safety Analysis Set and the Safety Analysis Set. Supportive listings will be provided.

All AEs leading to discontinuation recorded on the CRF will be listed for the Run-In Safety Analysis Set and the Safety Analysis Set. Additionally, TEAEs leading to dose reduction will be listed for the Safety Analysis Set.

Additionally, TEAEs leading to dose reduction will be listed for the Safety Analysis Set

9.6.1.4 Deaths

A table presenting the number and percentage of subjects who died during the Run-In period and during the open–label treatment period will be presented for the Run-In Safety Analysis Set and Safety Analysis Set, respectively. Deaths occurring in the study will also be listedfor all screened subjects.

9.6.1.5 Potentially Pertaining to Drug Withdrawal Symptoms

A summary of TEAEs potentially pertaining to drug withdrawal, as defined in Appendix 2, will be summarized by SOC and PT for the Safety Analysis Set.

9.6.1.6 Potentially Pertaining to Pancreatitis

A summary of TEAEs potentially pertaining to pancreatitis, as defined in Appendix 2, will be summarized by SOC and PT for the Safety Analysis Set.

9.6.1.7 Potentially Pertaining to Hepatic Disorders

A summary of TEAEs potentially pertaining to hepatic disorders, as defined in Appendix 2, will be summarized by SOC and PT for the Safety Analysis Set.

9.6.1.8 Potentially Pertaining to Injection Site Reactions

A summary of TEAEs potentially pertaining to injection site reactions, as defined in Appendix 2, will be summarized by SOC and PT for the Safety Analysis Set.

9.6.1.9 Potentially Pertaining to Respiratory Depression and Failure

A summary of TEAEs potentially pertaining to respiratory depression and failure, as defined in Appendix 2, will be summarized by SOC and PT for the Safety Analysis Set.

9.6.1.10 Potentially Pertaining to Central Nervous System Depression

A summary of TEAEs potentially pertaining to central nervous system depression, as defined in Appendix 2, will be summarized by SOC and PT for the Safety Analysis Set.

9.6.1.11 Potentially Pertaining to Orthostatic Hypotension

A summary of TEAEs potentially pertaining to orthostatic hypotension, as defined in Appendix 2, will be summarized by SOC and PT for the Safety Analysis Set.

9.6.2 Laboratory Data

Laboratory data will be reported using International System (SI) units as collected by the central laboratory. Unless otherwise specified, all continuous laboratory data will be summarized using descriptive statistics (n, mean, SD, median, min, and max) for each scheduled study assessment as well as change from baseline and percentage change from baseline [if applicable] by parameter class (hematology, chemistry, and urinalysis). The following parameters will have graphs of the mean values by visit through the end of study: hematocrit, alkaline phosphatase (ALP), alanine aminotransferase (ALT), amylase, lipase, trypsinogen, aspartate aminotransferase (AST), creatinine clearance, creatinine kinase, gamma-glutamyl transferase, and bilirubin (from serum chemistry results). All laboratory assessments include a baseline summary as defined in Section 5 unless otherwise indicated. Hematology, chemistry, and urinalysis data will be summarized by displaying shifts from baseline value (low/normal/high) to last assessment on treatment and worst result on treatment (for only subjects with normal as baseline) considering both scheduled and unscheduled assessments. All laboratory assessments will be listed by panel with the corresponding normal ranges for each parameter. Screening laboratory will be provided in a separate listing.

9.6.2.1 Hematology

Parameters include hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, pancreatic enzymes, absolute red blood cell count, and absolute white blood cell count. Visits include Week 1 Day 1, Week 3 Day 15, Week 5 Day 29, Week 7 Day 43, Week 9 Day 57, Week 11 Day 71, Week 13 Day 85, Week 15 Day 99, Week 17 Day 113, Week 19 Day 127, Week 21 Day 141, Week 25 Day 169, Week 29 Day 197, Week 33 Day 225, Week 37 Day 253, Week 41 Day 281, Week 45 Day 309, Week 49 Day 337, and end of study visit.

9.6.2.2 Serum Chemistry

Parameters include albumin, ALP, ALT, amylase, AST, blood urea nitrogen, calcium, calculated creatinine clearance, carbon dioxide, chloride, creatinine, creatinine kinase and subtypes, gamma-glutamyl transferase, globulin, glucose (non-fasting), high-density lipoprotein, immunoreactive trypsinogen, lactate dehydrogenase, lipase, low-density lipoprotein, magnesium, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, and uric acid. Visits include Week 1 Day 1, Week 3 Day 15, Week 5 Day 29, Week 7 Day 43, Week 9 Day 57, Week 11 Day 71, Week 13 Day 85, Week 15 Day 99, Week 17 Day 113, Week 19 Day 127, Week 21 Day 141, Week 25 Day 169, Week 29 Day 197, Week 33 Day 225, Week 37 Day 253, Week 41 Day 281, Week 45 Day 309, Week 49 Day 337, and end of study visit.

An additional summary of potential hepatotoxicity will be presented with the number and percentage of subjects at each time point and at any point on study that meet the following conditions: ALT > 3 × upper limit of normal (ULN), ALT >= 3 × ULN to <5 × ULN, ALT >= 5 × ULN to <8 × ULN, ALT>= 8 × ULN, AST > 3 × ULN, AST >= 3 × ULN to <5 × ULN, AST >= 5 × ULN to <8 × ULN, AST>= 8 × ULN, ALT > 3 × ULN and AST > 3 × ULN, ALT and AST >= 3 × ULN to <5 × ULN, ALT and AST >= 5 × ULN to <8 × ULN, ALT and AST >= 8 × ULN, Bilirubin >= 2 × ULN, Bilirubin >= 2 × ULN to <5 × ULN, Bilirubin >= 5 × ULN Hy's Law cases which is defined as AST > 3 × ULN or ALT > 3 × ULN, bilirubin > 2 × ULN, and ALP < 2 × ULN, and Modified Hy's Law which is defined as AST > 3 × ULN **AND** ALT > 3 × ULN, bilirubin > 2 × ULN, and ALP < 2 × ULN. A listing of these cases including the results for the parameters and the number of times the ULN each result is will be provided. Figures of ALT [× ULN] vs. total bilirubin [× ULN] and AST [× ULN] vs. total bilirubin [× ULN] on a log/log scale and box plots of AST, ALT, and total bilirubin will be presented

An additional summary of high values of amylase, lipase, and trypsinogen will be presented with the number and percentage of subjects at each time point and at any point on study that meet the following conditions: Amylase > 3 × upper limit of normal (ULN), Lipase > 3 × ULN, and Trypsinogen> ULN. A listing of these cases including the results for the parameters and the number of times the ULN each result is will be provided.

9.6.2.3 Urinalysis

Parameters include appearance, bilirubin, color, glucose, ketones, leucocyte esterase, nitrite, occult blood, pH, protein, specific gravity, and urobilinogen.

9.6.2.4 Urine Drug Screen

Parameters include: opioids, cocaine, amphetamines, methadone, cannabinoids, barbiturates, benzodiazepines, methamphetamine, and phencyclidine. All drugs detected in the urine drug screen will be listed.

9.6.3 Vital Signs

Measurements of vital signs (blood pressure systolic, blood pressure diastolic, pulse rate, oral temperature, pulse oximetry, weight, height, BMI, and waist-to-hip ratio) will be summarized using descriptive statistics at each scheduled visit and time point including change from baseline and percentage change from baseline.

Listings of all vital sign assessments will be provided in the following groups:

- Blood pressure systolic, blood pressure diastolic, pulse rate, oral temperature, and respiration rate
- Pulse Oximetry
- Body weight, BMI, and waist-to-hip ratio.

9.6.4 Other Safety Variables

9.6.4.1 12-lead Electrocardiograms

Results from 12-lead ECGs as determined by central reader will be categorized as normal or abnormal and will be summarized using shift from baseline to end of study/early termination using frequency counts. An additional table summarizing shift from baseline to worst result on study will be presented. ECG interval measurements including change from baseline will be summarized by time point using descriptive statistics for actual value and change from baseline. Parameters will include heart rate (beats/min), PR Interval (msec), QRS Duration (msec), RR interval (msec), QT interval (msec), adjudicated QTc-Bazett (msec), and adjudicated QTc-Fridericia (msec). Additionally, the number and percentage of subjects with a >30 msec or >60 msec change from baseline will be summarized by visit and at any point throughout the study. ECG results will be listed for interpretation and for the interval measurements.

9.6.4.2 Suicidality

Suicidal ideation and suicidal behavior responses (Yes/No) will be summarized using counts and percentages in the Safety Analysis Set. Shift tables to demonstrate changes in eC-SSRS categories and changes in suicidal ideation and behavior scores, as defined in Section 5 from baseline during the open-label treatment period will be presented. eC-SSRS and suicidal ideation responses will be listed separately. The suicidal ideation intensity ratings, each of the five items and the total score of the intensity for subjects with an ideation will be listed.

Several subjects completed the baseline-lifetime version of the e-CSSRS questionnaire that was intended to be used at Screening rather than the 'since last visit' version **required at** all subsequent visits. The data collected using the wrong version will be presented in the listings, but will not presented in the summary tables.

9.6.4.3 Local Injection Site Tolerability

Local injection site tolerability as assessed by the Injection Site Grading scale will be summarized by category (pain, tenderness, erythema/redness, induration, and swelling) and severity at each time point and at any time using frequency counts and percentages.

A separate listing will be presented for severe/life threatening responses with their corresponding VAS scores.

The injection site tolerability results will be listed.

9.6.4.4 Injection Site Pain

Injection Site Pain VAS scores will be summarized by subject type, injection, and time point after injection. The burning/stinging categorical variable (Yes/No) will be summarized by percentage of responses in each subject type at each time point. Attempted removal results will be summarized by percentage of subjects with attempted removal in each subject type at each visit.

Separate listings for burning/stinging and attempted removal evaluations will be provided. A listing of injection site pain VAS scores will also be provided.

9.6.4.5 Other Safety Variables

Urine pregnancy results will be listed.

9.7 Pharmacokinetic Analysis

A listing of the PK data, including buprenorphine and norbuprenorphine plasma concentration measurement, will be provided. The population PK analysis of the drug plasma concentration data will be reported separately.

10.0 Validation

PRA's goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

11.0 References

United States Department of Health and Human Services: Food and Drug Administration. Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. October 2005.

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
ADY	Analysis Day
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CDF	Cumulative Distribution Function
CRF	Case Report Form
COWS	Clinical Opioid Withdrawal Scale
CTMS	Clinical Trials Management System
eC-SSRS	Electronic Columbia Suicide Severity Rating Scale
ECG	Electrocardiogram
EOS	End of Study
ET	Early Termination
IA	Interim Analysis
IDC	Individual Drug Counseling
MedDRA	Medical Dictionary for Regulatory Activities
PDV	Protocol Deviation
PK	Pharmacokinetic
PT	Preferred Term
RBP	Reckitt Benckiser Pharmaceuticals Inc.
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SI	International System
SOC	System Organ Class
SOWS	Subjective Opioid Withdrawal Scale
TEAE	Treatment-Emergent Adverse Event
TLFB	Timeline Followback

TFLs	Tables, Listings, and Figures
UDS	Urine Drug Screen
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WHODRUG	World Health Organization Drug Dictionary

Appendix 2 List of Preferred Terms from Standard MedDRA Queries for Adverse Events of Special Interest

Adverse Events Potentially Pertaining to Pancreatitis

Preferred Terms Potentially Pertaining to Pancreatitis		
Amylase abnormal	Hyperbilirubinaemia	Pancreatic haemorrhage
Amylase creatinine clearance ratio abnormal	Hyperlipasaemia	Pancreatic necrosis
Amylase increased	Ischaemic pancreatitis	Pancreatic phlegmon
Bilirubin conjugated abnormal	Lipase abnormal	Pancreatic pseudocyst
Blood bilirubin increased	Lipase increased	Pancreatic pseudocyst drainage
Blood trypsin increased	Lipase urine increased	Pancreatitis
Cullen's sign	Oedematous pancreatitis	Pancreatitis acute
Grey Turner's sign	Pancreatic abscess	Pancreatitis haemorrhagic
Haemorrhagic necrotic pancreatitis	Pancreatic enzyme abnormality	Pancreatitis necrotising
Hereditary pancreatitis	Pancreatic enzymes abnormal	Pancreatitis relapsing
Hyperamylasaemia	Pancreatic enzymes increased	Pancreatorenal syndrome

Adverse Events Potentially Pertaining to Respiration Depression and Failure

Preferred Terms Potentially Pertaining to Respiratory Depression and Failure		
Acute respiratory distress syndrome	Hypopnoea	Respiratory depression
Acute respiratory failure	Hypoventilation	Respiratory depth decreased
Apnoea	Hypoventilation neonatal	Respiratory distress
Apnoea neonatal	Lung hypoinflation	Respiratory failure
Infantile apnoea	Meconium aspiration syndrome	Respiratory paralysis
Apnoeic attack	Neonatal respiratory arrest	Respiratory rate decreased
Bradypnoea	Neonatal respiratory depression	Severe acute respiratory syndrome
Breath sounds absent	Neonatal respiratory distress syndrome	Cardio-respiratory arrest
Cardio-respiratory distress	Neonatal respiratory failure	Cardio-respiratory arrest neonatal
Central-alveolar hypoventilation	Respiratory arrest	Cardiopulmonary failure
Chronic respiratory failure		

Adverse Events Potentially Pertaining to Central Nervous System Depression

Preferred Terms Potentially Pertaining to Central Nervous System Depression		
Mental fatigue	Postictal state	Psychomotor seizures
Microsleep	Consciousness fluctuating	Simple partial seizures
Narcolepsy	Neonatal oversedation	Autonomic seizure
Coma	Hypoglycaemic unconsciousness	Atonic seizures
Impaired driving ability	Hyperglycaemic unconsciousness	Seizure
Impaired ability to use machinery	Post-injection delirium sedation syndrome	Partial seizures with secondary generalisation
Accident	Preictal state	Alcoholic seizure
Road traffic accident	Psychogenic pseudosyncope	Partial seizures
Vision blurred	Mental status changes	Seizure like phenomena
Vertigo CNS origin	Mental status changes postoperative	Seizure cluster
Incoherent	Slow response to stimuli	Change in seizure presentation
Disturbance in attention	Unresponsive to stimuli	Migraine-triggered seizure
Judgement impaired	Hyporesponsive to stimuli	Psychogenic seizure
Mental impairment	Benign familial neonatal convulsions	Seizure anoxic
Borderline mental impairment	Febrile convulsion	Post stroke seizure
Cognitive disorder	Drug withdrawal convulsions	Accidental death
Altered state of consciousness	Convulsion neonatal	Accidental overdose
Depressed level of consciousness	Convulsions local	Accidental exposure to product
Lethargy	Tonic convulsion	Cerebrovascular accident
Loss of consciousness	Convulsion in childhood	Dizziness
Sedation	Clonic convulsion	Dizziness exertional
Somnolence	Acute encephalitis with refractory, repetitive partial seizures	Dizziness postural
Somnolence neonatal	Generalised tonic-clonic seizure	Procedural dizziness
Stupor	Complex partial seizures	Neurotoxicity
Syncope		

Adverse Events Potentially Pertaining to Orthostatic Hypotension

Preferred Terms Potentially Pertaining to Orthostatic Hypotension		
Orthostatic hypotension	Vision blurred	Dizziness
Dizziness exertional	Dizziness postural	Syncope
Presyncope	Diastolic hypotension	Hypotension

Adverse Events Potentially Pertaining to Drug Withdrawal Symptoms

Preferred Terms Potentially Pertaining to Drug Withdrawal Symptoms		
Agitation	Hypertension	Piloerection
Anxiety	Hypervigilance	Pruritus
Arthralgia	Influenza like illness	Psychomotor hyperactivity
Bone pain	Insomnia	Pyrexia
Chills	Irritability	Respiratory rate increased
Decreased appetite	Lacrimal disorder	Restlessness
Depression	Lacrimation increased	Rhinitis
Diarrhoea	Malaise	Rhinorrhoea
Dizziness	Muscle spasms	Sneezing
Drug dependence	Muscle twitching	Tachycardia
Flushing	Myalgia	Tremor
Heart rate increased	Mydriasis	Vomiting
Hyperhidrosis	Nausea	Yawning
Drug Withdrawal Syndrome		

Adverse Events Potentially Pertaining to Hepatic Events

Preferred Terms Potentially Pertaining to Hepatic Events		
Bilirubin excretion disorder	Oesophageal varices haemorrhage	Galactose elimination capacity test decreased
Cholaemia	Peripancreatic varices	Gamma-glutamyltransferase abnormal
Cholestasis	Portal fibrosis	Gamma-glutamyltransferase increased
Cholestatic liver injury	Portal hypertension	Guanase increased
Cholestatic pruritus	Portal hypertensive enteropathy	Hepaplastin abnormal
Drug-induced liver injury	Portal hypertensive gastropathy	Hepaplastin decreased
Hepatitis cholestatic	Portal vein cavernous transformation	Hepatic artery flow decreased
Hyperbilirubinaemia	Portal vein dilatation	Hepatic congestion
Icterus index increased	Portopulmonary hypertension	Hepatic enzyme abnormal
Jaundice	Renal and liver transplant	Hepatic enzyme decreased
Jaundice cholestatic	Retrograde portal vein flow	Hepatic enzyme increased
Jaundice hepatocellular	Reye's syndrome	Hepatic function abnormal
Mixed liver injury	Reynold's syndrome	Hepatic hydrothorax
Ocular icterus	Splenic varices	Hepatic hypertrophy
Parenteral nutrition associated liver disease	Splenic varices haemorrhage	Hepatic mass
Deficiency of bile secretion	Steatohepatitis	Hepatic pain
Yellow skin	Subacute hepatic failure	Hepatic sequestration
Acute hepatic failure	Varices oesophageal	Hepatic vascular resistance increased

Acute on chronic liver failure	Varicose veins of abdominal wall	Hepatobiliary scan abnormal
Acute yellow liver atrophy	Anorectal varices	Hepatomegaly
Ascites	Anorectal varices haemorrhage	Hepatosplenomegaly
Asterixis	Intrahepatic portal hepatic venous fistula	Hyperammonaemia
Bacterascites	Peritoneovenous shunt	Hyperbilirubinaemia
Biliary cirrhosis	Portal shunt	Hypercholia
Biliary cirrhosis primary	Portal shunt procedure	Hypertransaminasaemia
Biliary fibrosis	Small-for-size liver syndrome	Kayser-Fleischer ring
Cholestatic liver injury	Spider naevus	Liver function test abnormal
Chronic hepatic failure	Splenorenal shunt	Liver induration
Coma hepatic	Splenorenal shunt procedure	Liver palpable
Cryptogenic cirrhosis	Spontaneous intrahepatic portosystemic venous shunt	Liver scan abnormal
Diabetic hepatopathy	Stomal varices	Liver tenderness
Drug-induced liver injury	Acute graft versus host disease in liver	Mitochondrial aspartate aminotransferase increased
Duodenal varices	Allergic hepatitis	Molar ratio of total branched-chain amino acid to tyrosine
Gallbladder varices	Autoimmune hepatitis	Oedema due to hepatic disease
Gastric variceal injection	Chronic graft versus host disease in liver	Perihepatic discomfort
Gastric variceal ligation	Chronic hepatitis	Retrograde portal vein flow
Gastric varices	Graft versus host disease in liver	Total bile acids increased
Gastric varices haemorrhage	Hepatitis	Transaminases abnormal
Hepatectomy	Hepatitis acute	Transaminases increased
Hepatic atrophy	Hepatitis cholestatic	Ultrasound liver abnormal
Hepatic calcification	Hepatitis chronic active	Urine bilirubin increased
Hepatic cirrhosis	Hepatitis chronic persistent	X-ray hepatobiliary abnormal
Hepatic encephalopathy	Hepatitis fulminant	5'nucleotidase increased
Hepatic encephalopathy prophylaxis	Hepatitis toxic	Blood alkaline phosphatase abnormal
Hepatic failure	Ischaemic hepatitis	Blood alkaline phosphatase increased
Hepatic fibrosis	Lupus hepatitis	Blood cholinesterase abnormal
Hepatic hydrothorax	Non-alcoholic steatohepatitis	Blood cholinesterase decreased
Hepatic infiltration eosinophilic	Radiation hepatitis	Deficiency of bile secretion
Hepatic lesion	Steatohepatitis	Glutamate dehydrogenase increased
Hepatic necrosis	Granulomatous liver disease	Haemorrhagic ascites
Hepatic steato-fibrosis	Liver sarcoidosis	Hepatic fibrosis marker abnormal
Hepatic steatosis	Portal tract inflammation	Hepatic fibrosis marker increased
Hepatitis fulminant	Alanine aminotransferase abnormal	Hypoalbuminaemia
Hepatobiliary disease	Alanine aminotransferase increased	Leucine aminopeptidase increased
Hepatocellular foamy cell syndrome	Ammonia abnormal	Liver function test decreased
Hepatocellular injury	Ammonia increased	Liver function test increased

Hepatopulmonary syndrome	Ascites	Liver iron concentration abnormal
Hepatorenal failure	Aspartate aminotransferase abnormal	Liver iron concentration increased
Hepatorenal syndrome	Aspartate aminotransferase increased	Model for end stage liver disease score abnormal
Hepatotoxicity	Bacterascites	Model for end stage liver disease score increased
Intestinal varices	Bile output abnormal	Periportal oedema
Intestinal varices haemorrhage	Bile output decreased	Peritoneal fluid protein abnormal
Liver and small intestine transplant	Biliary ascites	Peritoneal fluid protein decreased
Liver dialysis	Bilirubin conjugated abnormal	Peritoneal fluid protein increased
Liver disorder	Bilirubin conjugated increased	Pneumobilia
Liver injury	Bilirubin urine present	Portal vein flow decreased
Liver operation	Biopsy liver abnormal	Portal vein pressure increased
Liver transplant	Blood bilirubin abnormal	Retinol binding protein decreased
Lupoid hepatic cirrhosis	Blood bilirubin increased	Urobilinogen urine decreased
Minimal hepatic encephalopathy	Blood bilirubin unconjugated increased	Urobilinogen urine increased
Mixed liver injury	Bromosulphthalein test abnormal	Alcoholic liver disease
Nodular regenerative hyperplasia	Child-Pugh-Turcotte score abnormal	Cirrhosis alcoholic
Non-alcoholic fatty liver	Child-Pugh-Turcotte score increased	Fatty liver alcoholic
Non-alcoholic steatohepatitis	Computerised tomogram liver	Hepatic steato-fibrosis
Non-cirrhotic portal hypertension	Foetor hepaticus	Hepatitis alcoholic
Oedema due to hepatic disease	Galactose elimination capacity test abnormal	Zieve syndrome

Adverse Events Potentially Pertaining to Injection Site Reactions

Preferred Terms Potentially Pertaining to Injection Site Reactions		
Immediate post-injection reaction	Injection site irritation	Injection site movement impairment
Injection related reaction	Injection site mass	Injection site lymphadenopathy
Injection site abscess	Injection site necrosis	Injection site nodule
Injection site cellulitis	Injection site nerve damage	Embolia cutis medicamentosa
Injection site infection	Injection site oedema	Injection site scar
Injection site pustule	Injection site pain	Injection site discharge
Injection site abscess sterile	Injection site paraesthesia	Injection site pallor
Injection site anaesthesia	Injection site phlebitis	Injection site papule
Injection site atrophy	Injection site pruritus	Injection site injury
Injection site bruising	Injection site rash	Injection site scab
Injection site cyst	Injection site reaction	Injection site eczema
Injection site dermatitis	Injection site thrombosis	Injection site streaking
Injection site erosion	Injection site ulcer	Injection site dryness
Injection site erythema	Injection site urticaria	Injection site laceration
Injection site extravasation	Injection site vesicles	Injection site macule
Injection site fibrosis	Injection site warmth	Injection site vasculitis
Injection site granuloma	Injection site ischaemia	Injection site exfoliation
Injection site haematoma	Injection site coldness	Injection site dysaesthesia
Injection site haemorrhage	Injection site discolouration	Injection site plaque
Injection site hypersensitivity	Injection site photosensitivity reaction	Injection site hyperaesthesia
Injection site hypertrophy	Injection site swelling	Injection site hypoaesthesia
Injection site induration	Injection site discomfort	Injection site hypertrichosis
Injection site inflammation	Injection site calcification	

Appendix 3 List of Post-text Tables, Figures, Listings, and Supportive SAS Output Appendices

The TFL shells and table of contents for this study are provided in a separate document titled “Indivior 130003 SAP TFLs Version 3.0”.