NCT02896296

Study Number: INDV-6000-301

Title: An Open-Label, Depot Buprenorphine (RBP-6000) Treatment Extension Study in Subjects With Opioid Use Disorder

Statistical Analysis Plan Date: 06 October 2017

Statistical Analysis Plan

Sponsor:	Indivior Inc.
Protocol No:	INDV-6000-301
Protocol Version No./Date	Amendment 1 / 30-Sep-2016
Title	An Open-Label, Depot Buprenorphine (RBP-6000) Treatment Extension Study in Subjects with Opioid Use Disorder
CRF Version No./Date	5.0 / 17 Mar 2017
SAP Version No./Date:	1.0 / 06 Oct 2017

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1.0 TITLE PAGE

INDV-6000-301

An Open-Label, Depot Buprenorphine (RBP-6000) Treatment Extension Study in Subjects with Opioid Use Disorder

Final Version 1.0: October 6, 2017

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CDF	Cumulative Distribution Function
CNS	Central nervous system
CRF	Case Report Form
CTMS	Clinical Trials Management System
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	Electrocardiogram
EOS	End of Study
ET	Early Termination
GGT	Gamma-glutamyl Transpeptidase
HDL-C	High-density lipoprotein - Cholesterol
IA	Interim Analysis
ICF	Informed Consent Form
IDC	Individual Drug Counseling
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over The Counter
PDV	Protocol Deviation
PT	Preferred Term
OUD	Opioid Use Disorder
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
SUSAR	Suspected Unexpected Serious Adverse Event
TBIL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Listings, and Figures
UDS	Urine Drug Screen

ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WHODRUG	World Health Organization Drug Dictionary

4.0 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 INDV-6000-301).

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 30SEP2016 and CRF dated 17Mar2017.

This is a multicenter, open-label, RBP-6000 treatment extension study in which approximately 300 subjects diagnosed with moderate to severe Opioid Use Disorder (OUD) will be enrolled. Enrollment is defined as the first dose of RBP-6000 administered for this study. Only subjects who have completed the End of Study (EOS) procedures for Study RB-US-13-0003, have signed the INDV-6000-301 informed consent form (ICF), and meet all enrollment criteria will be considered for inclusion in this study.

The Institutional Review Board (IRB) approved ICF may be shared with the potential subject up to 2 months before the EOS Visit for Study RB-US-13-0003 to discuss this study as a possible treatment option. However, the ICF for Study INDV-6000-301 must not be signed until all assessments for the RB-US-13-0003 EOS Visit are complete.

The RB-US-13-0003 EOS assessments completed at the EOS Visit will serve as part of the screening assessments for this study. In addition, medical history will be collected, height measured, and subjects will be requested to complete a Columbia Suicide Severity Rating Scale (C-SSRS) baseline survey.

On Day 1 (the date of the first injection), eligible subjects will receive a subcutaneous (SC) injection of RBP-6000. For each injection, subjects may receive either 100 mg or 300 mg of RBP-6000 (to be referred to as 100/300 Flex for the remainder of this document), based on the medical judgment of the investigator. Following RBP-6000 injection, vital signs and the injection site will be assessed. The injection site will be assessed by the site for pain, tenderness, erythema/redness, induration and swelling using a 5-point severity scale (the Injection Site Grading Scale). In addition, the subject will assess their own injection site pain using a visual analog scale (VAS) (referred to as the Injection Site Pain VAS). Before departing the site, the subject will also be assessed for adverse events (AEs) and use of concomitant medications.

Subjects will not be permitted to receive supplemental buprenorphine during the RBP-6000 treatment period (Day 1 to EOS/ET Visit). Subjects who require supplemental buprenorphine pharmacotherapy during the RBP-6000 treatment period will be withdrawn from the study and referred for appropriate treatment.

Subjects will return to the site for monthly injection visits every 28 days (-2 / +7 days) for a total of up to 6 injections. Subjects are not required to complete all 6 injections and may choose to “early terminate” (ET) the study at any time.

At each subsequent visit (Injection Visits 2 through 6) the following procedures and assessments will be performed: urine pregnancy test for all female subjects who are of childbearing potential before each injection; evaluation of previous injection site for potential reaction and evidence of attempts to remove the depot; collection of vital signs pre- and post-injection; RBP-6000 injection; urine drug screen (UDS); C-SSRS since last visit, counseling (manual-guided behavioral therapy); local injection site grading; subject self-assessment of injection site pain (Injection Site Pain VAS); use of concomitant medications; and assessment for AEs. Laboratory tests (hematology, chemistry and urinalysis) may be requested by the investigator on an ad-hoc basis as necessary to further examine any AEs.

Alternative treatment options should be assessed at least two months before EOS at each visit, however it is recommended where possible to assess at every visit.

At the EOS/ET Visit, the following procedures and assessments will be performed: urine pregnancy test for all female subjects who are of childbearing potential; evaluation of previous injection site for potential reaction and evidence of attempts to remove the depot; vital sign measurements; UDS; C-SSRS since last visit, counseling (manual-guided behavioral therapy); use of concomitant medications; assessment for AEs; brief physical exam; body weight measurement (to determine a subject's body mass index [BMI]); hip and waist circumference measurement (to determine a subject's hip-to-waist ratio); and laboratory tests (hematology, chemistry, urinalysis).

Approximately 4 weeks after EOS/ET Visit, all subjects should be contacted by telephone or face-to-face visit safety follow-up assessment of AEs and use of any concomitant medications.

5.0 OBJECTIVE

Indivior is developing RBP-6000, a long-acting formulation of buprenorphine for monthly subcutaneous (SC) injection, for the treatment of Opioid Use Disorder (OUD).

The objective is to provide ongoing treatment with RBP-6000 and safety monitoring for subjects who complete the RB-US-13-0003 study and for whom a new treatment venue has not been identified or arranged.

6.0 SUBJECT POPULATIONS AND TREATMENT GROUPS

6.1 SCREENED POPULATION

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

6.2 SAFETY ANALYSIS SET

The Safety Analysis Set consists of all subjects who received at least one dose of RBP-6000.

6.3 TREATMENT GROUPS

There is only one treatment group in the trial and all subjects will be labeled with "RBP-6000 (100/300 mg Flex)".

7.0 SUBJECT DISPOSITION

The number and percentage of subjects screened and screen failures, if any, will be summarized.

The number and percentage of subjects who entered the RBP-6000 treatment period (i.e., Treatment Period, and see definition in Section 20.1), 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 along with reasons for study discontinuation will be summarized.

In summary, it is that the following number and percentage of subjects will be presented:

- All subjects who were considered screen-failures
- All subjects who entered the RBP-6000 treatment period (i.e., Treatment Period, and see definition in Section 20.1)
  - All subjects who completed the study
  - All subjects who prematurely discontinued from the RBP-6000 treatment period along with reasons for study discontinuation.

The number and percentage of subjects included in each analysis set will be presented.

A listing of the inclusion/exclusion reasons for screen failures will be provided, if any.

8.0 PROTOCOL DEVIATIONS

A listing of important protocol deviations (PDV) will be presented by subject using the Safety Analysis Set. An important deviation is defined as:

- Subject was deemed eligible for the study but did not meet inclusion/exclusion criteria
- Consent was not obtained from the subject

9.0 DEMOGRAPHICS AND OTHER 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[cm], hip[cm], waist-to-hip ratio and body mass index [BMI; kg/m2]) will be summarized using descriptive statistics for subjects in the Safety Analysis Set. Qualitative variables (sex, ethnicity, race, age categories, BMI categories) will be summarized using frequencies while quantitative variables (age, weight, height, BMI, waist, hip and waist-to-hip ratio) will be summarized using mean, SD, median, minimum, and maximum. Demographic and baseline data will also be listed for all subjects.

9.1 SUBSTANCE USE HISTORY

Substance use history will be presented by substance and previous use for subjects in the Safety Analysis Set. Tobacco use [never, former, current], caffeine use [never, former, current], alcohol use [never, former, current]) will be summarized using descriptive statistics for subjects in the Safety Analysis Set. Qualitative variables (tobacco use, caffeine use, alcohol use) will be summarized using frequencies.

9.2 MEDICAL HISTORY

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 and summarized by the number and percentage of subjects in each System Organ Class (SOC), Preferred Term (PT) and in the Safety Analysis Set. Subjects will be counted only once for each PT, only once at the System Organ Class (SOC), and only once at subject level for the counting of total number of subjects with a medical history term. Counts will be presented in descending frequency unless otherwise specified.

Listings of medical history events for each subject will be provided.

9.3 PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be categorized by preferred name and drug category class (CMCLAS, ATC level 4 class per World Health Organization Drug Dictionary [WHODRUG]); and 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.

Prior medications rolling over from prior studies will be considered for both prior and concomitant medications in this study.

Prior Medications

For a subject in the Safety Analysis Set, prior medications will include any medication taken within 28 days prior to subject's first dose of RBP-6000 in the INDV-6000-301 study.

Concomitant Medications

Concomitant medications are defined as prescribed medications and Over The Counter (OTC) preparations, including herbal preparations and vitamins, other than RBP-6000.

All prior medications will be presented in separate listing for the Safety Analysis Set.

A summary of all concomitant medications taken from Day 1 to last dose + 28 days will be presented as during RBP-6000 dosing for the Safety Analysis Set.

A summary of all concomitant medications taken from the last dose + 29 days to the last recorded assessment will be presented as post RBP-6000 dosing for the Safety Analysis Set.

A listing of all subject's concomitant medications during RBP-6000 dosing and post RBP-6000 dosing will be listed separately.

After imputing the incomplete start/end date of non-study medications (as described in Section 20.8), the determination of concomitant medication during vs. post RBP-6000 dosing follows the rules in the Table 1 below.

Table 1: Determination of Concomitant Medication during vs. Post RBP-6000 doing

		Start date of Non-Study Medication			
		missing	Prior to day 1	from Day 1 to last dose +28 days (inclusive)	Post last dose+28 days
End date of non-study medication	missing	During[1], Post[2]	During, Post	During, Post	Post
	from Day 1 to last dose +28 days (inclusive)	During	During	During	Data error
	Post last dose+28 days	During, post	During, post	During, post	post

[1] during RBP-6000 dosing. [2] post RBP-6000 dosing

CNS Depressants

If a subject satisfies any of the three criteria below, then the subject is classified as taking a CNS Depressant

Criterion 1:

Subject with concomitant medication and its class (CMCLAS) in ('BENZODIAZEPINE RELATED DRUGS' 'BENZODIAZEPINE DERIVATIVES' 'DIAZEPINES, OXAZEPINES, THIAZEPINES AND OXEPINES' 'OTHER HYPNOTICS AND SEDATIVES' 'PHENOBARBITAL'). Defined in the later section (CNS Depressant Medication Categories)

Criterion 2:

Subject with substances 'Barbiturates' or 'Benzodiazepine' detected positive in Urine Drug Screen during the Treatment Period.

CNS Depressant Medication Categories

Benzodiazepine-related drugs

If the Concomitant medication class is "BENZODIAZEPINE RELATED DRUGS" or detection of substances "Benzodiazepine" positive in Urine Drug Screen positive during the Treatment Period, then it is derived as Benzodiazepine related drugs.

Benzodiazepine derivatives

If the Concomitant medication class contains ("BENZODIAZEPINE DERIVATIVES", "DIAZEPINES, OXAZEPINES, THIAZEPINES AND OXEPINES") during the Treatment Period then it is derived as Benzodiazepine Derivatives.

Other Hypnotics and Sedatives

If the Concomitant medication class is ("OTHER HYPNOTICS AND SEDATIVES") during the Treatment Period, then it is derived as Other Hypnotics and Sedatives.

Phenobarbital and Derivatives

If the Concomitant medication class is "PHENOBARBITAL" during RBP-600 dosing or detection of substances Barbiturates positive in Urine Drug Screen during the Treatment Period, then it is derived as Phenobarbital and Derivatives.

Summary of subjects who have taken CNS depressant medications during RBP-6000 dosing (from Day 1 to last dose + 28 days) be provided. CNS depressant medications can be indemnified from two sources in this study: Concomitant medications or Urine Drug Screen as in the table below (Table 2).

Table 2: Summary of Subjects Who Have Taken CNS Depressant Medications During RBP-6000 Dosing

Any CNS depressant (from Concomitant medications) taken with a start date after Day 1 to last dose + 28 days
Benzodiazepine-related Drugs Benzodiazepines Derivatives Other Hypnotics and Sedatives Phenobarbital and Derivatives
Any positive CNS depressant (from UDS) during the treatment period
Barbiturate Positive Benzodiazepines Positive

Preferred terms at drug class ATC level 3 of drug categories Benzodiazepine-related Drugs, Benzodiazepines Derivatives, Other Hypnotics and Sedatives and Phenobarbital and Derivatives will be summarized in the safety analysis set (see Appendix 1 for the list of CNS depressant medications).

A separate table for CNS depressant medications will be summarized for post RBP-6000 dosing

CYP3A4 Inhibitor Medication Categories

The following four categories (Unclassified, Weak, Moderate and Strong) are used from Appendix 2 containing Generic/Brand name of the CYP3A4 Inhibitor medication and its categories.

Preferred terms at drug class ATC level 3 of CYP3A4 Inhibitor Medications (Unclassified, Weak, Moderate or Strong inhibitors) during RBP-6000 dosing and post RBP-6000 dosing will be summarized in separate tables.

10.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

10.1 EXTENT OF EXPOSURE

Exposure duration is defined as the date of last injection + 28 days - the date of first injection +1.

A summary of the exposure to RBP-6000 during the treatment period will be summarized by visit and dosage for the Safety Analysis Set. A listing of RBP-6000 exposure (administration/dispensation) will be provided.

The duration of exposure in 4 week intervals (i.e., 0 - <4 weeks, 4 - <8 weeks through 20 - <24 weeks and >= 24 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 by dose received in the Safety Analysis Set. RBP-6000 exposure data will also be listed detailing the dose of RBP-6000 received at each injection and days since last injection. Besides, the cumulative frequency distribution will be tabulated by categories of >0 weeks, >=4 weeks through >=24 weeks.

The number of subjects who had an early surgical removal of the RBP-6000 depot will be presented for the Safety Analysis Set and by dose level (i.e., either 100 mg or 300 mg). Early surgical removal of the study drug depot data including the reason and surgical removal date and time will be listed, if surgical removal of the RBP-6000 depot occurs within the study.

10.2 INJECTION DOSE AND VISIT COMPLIANCE

Number and percentage of subjects with injection administrated at each visit will be tabulated in the Safety Analysis Set. Cumulative frequency distribution of injections will be summarized.

Dose level frequency distribution (either 100 mg or 300 mg) at each visit will be summarized. Dose level over time during the treatment period for subjects who received 100 mg at the first injection and 300 mg at the first injection will be summarized respectively in the Safety Analysis Set.

Dose modification and its reason (adverse event, lower dose strategy or other) over time will be summarized and its distribution per visit will be plotted using stacked-bar plot. Listing of all subjects who experienced dose adjustments should be provided, including dose prior to and after dose adjustment, and reason for dose adjustment.

Days since last injection will be summarized in the safety analysis set and the distribution of the relative study days of injections will be plotted and listed.

11.0 EXPLORATORY EFFICACY ANALYSES

11.1 URINE DRUG SCREEN (UDS)

The urine sample collected at Screening visit will be tested for drugs listed in the Table 3. The drugs classified as opioids are identified in the same table.

Table 3: Opioid Drug Classification in Urine Drug Screen at Screening Visit.

Drug	Opioid?
Amphetamine	No
Barbiturates	No
Benzodiazepine	No
Benzoylecgonine (Cocaine metabolite)	No
Cannabinoids	No
Opiates	Yes
Codeine	Yes
Hydrocodone	Yes
Hydromorphone	Yes
Methadone	Yes
Morphine	Yes
Oxycodone	Yes
Oxymorphone	Yes
Methamphetamine	No
Phencyclidine	No

At Screening, specific substances were confirmed once the test for Opiates was positive.
The UDS for Opioids at Screening will be defined as follows:
The UDS for Opioids is Non-negative at Screening if at least one UDS result (listed in Table) is positive;
The UDS for Opioids is Negative at Screening, if all non-missing UDS results for opioids are negative.
If all UDS measurements for opioids are missing at Screening, the UDS for Opioids will be classified as missing; then be imputed as Non-negative; and be flagged as "Non-Responder Imputation".

The urine sample collected at visits in the Treatment Period will be tested for drugs listed in the Table 4. The drugs classified as opioids are identified in the same table.

Table 4: Opioid Drug Classification in Urine Drug Screen at visits in the Treatment Period

Drug	Opioid?
Amphetamine	No
Barbiturates	No
Benzodiazepine	No
Benzoylecgonine (Cocaine metabolite)	No
Cannabinoids	No
Opiates	Yes
Methadone	Yes
Oxycodone	Yes
Methamphetamine	No
Phencyclidine	No

Different from Screening Visit, specific opiate substances were not confirmed when the Opiates test was positive. Samples were tested for Oxycodone and Methadone separately from the Opiates test.

The UDS for Opioids at visits in the Treatment Period will be defined as follows:
The UDS for Opioids is Non-negative at visits in the Treatment Period if at least one UDS result (listed in Table 4; either the Opiates test, or individual test for Methadone or individual test for Oxycodone) is positive;
The UDS for Opioids is Negative at visits in the Treatment Period, if all non-missing UDS results for opioids are negative.
If all UDS measurements for opioids are missing at visits in the Treatment Period, the UDS for Opioids will be classified as missing; and then be imputed as Non-negative; and be flagged as "Non-Responder Imputation".

The percentage of UDS Negative for Opioids during the Treatment Period (i.e., only for scheduled visits in the Treatment Period) will be calculated by subject, as the number of visits with UDS Negative for Opioid for that subject divided by the number of scheduled visits during the Treatment Period. Note that this means that subject missing UDS for Opioids for any scheduled visit will be classified as Non-negative for that visit.
The subject-specific percentage of UDS Negative for opioids will be summarized using Descriptive statistics (n, mean (SD), median, min and max). The cumulative distribution function (CDF) will be tabulated for the following categories: >=0%, >=10%, >=20% through 100%.

A subject is classified as 'treatment success', if his/her percentage of UDS Negative for Opioids is >=80% during the Treatment Period. The Number and percentage of treatment successes will be summarized

The number and percentage of subjects with UDS Negative for Opioids by visit at Screening/Baseline or during the Treatment Period will be summarized. The denominator

of the percentage will be the number of subjects in the Safety Analysis Set. Additionally, the percentage of subjects with UDS Negative for Opioids by visit will also be calculated using the available data approach, where the subjects missing UDS for Opioids for a visit will be excluded from the denominator of the percentage for that visit.

The number and percentage of subjects with positive UDS results will be summarized for the substances tested or for Opiates test during the Treatment Period. The subject will be classified as positive for available substance/Opiates if the UDS result for that substance/Opiates is reported as positive at least once during the Treatment Period. Note that the subjects are only counted once for each substance or for the Opiates test.

All drugs detected in the UDS tests (either Negative or Non-negative) for each subject, for all visits (scheduled or unscheduled), will be listed.

12.0 SAFETY ANALYSES

All analyses will be conducted by Analysis Period (s) over time at each analysis visit or overall in the Safety Analysis Set. Please see definition for Analysis Period and Analysis Visit in Section 20.1 and 20.2 respectively.

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 Safety Variables are:

- Medical history.
- Urine pregnancy test.
- Suicidality using the C-SSRS.
- Prior and concomitant medications.
- Local injection site tolerability (e.g., injection site grading).
- Injection site pain using a subject-reported VAS.
- Weight, BMI, waist circumference, hip circumference and waist-to-hip ratio.
- Behavioral therapy.

12.1 ADVERSE EVENTS

12.1.1 Adverse Events

Imputation rules for AE (for determination of TEAE only) start date are in Section 20.7.

Treatment-emergent Adverse Events (TEAEs)

TEAEs are those that started following the first dose of RBP-6000 and before the Treatment End Date (the maximum of the date of the end-of-study/ Early Termination (EOS/ET) visit and the date of last injection + 28 days) in this study, or were present prior to the first dose of RBP-6000 regardless of causality and increased in severity within the treatment period (defined in section 20.1) AEs include those events that are ongoing at the time a subject rolls-over from the RB-US-13-0003.

Treatment-related Adverse Events

A summary of TEAEs will be presented for the Safety Analysis Set, including the number and percentage of subjects reporting at least one TEAE, the number and percentage of subjects with the following:

- Related TEAEs
- SAEs
- Related SAEs
- TEAEs with an outcome of death
- TEAEs
- Severe TEAEs
- TEAEs leading to RBP-6000 discontinuation

A breakdown of the number and percentage of subjects reporting each TEAE categorized by SOC and PT coded per the MedDRA dictionary version 19.0 will be presented in the Safety Analysis Set. Note that counting will be by subject not by event and subjects will be only counted once within each SOC or PT.

A further tabulation of events experienced by ≥5% of subjects by SOC and PT will be presented for the Safety Analysis Set. If there are no TEAEs experienced ≥5% of subjects by any PT, this table will be empty.

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

12.1.2 Serious Adverse Events

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

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

12.1.3 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 Safety Analysis Set. Supportive listings will be provided.

All AEs leading to discontinuation recorded on the CRF will be listed. Additionally, TEAEs leading to dose reduction will be listed.

12.1.4 Deaths

A table presenting the number and percentage of subjects who died during the Treatment Period will be presented for the Safety Analysis Set, respectively. Deaths occurring in the study will also be listed for all screened subjects, if death occurs within the study.

12.1.5 Potentially Pertaining to Drug Withdrawal Symptoms

A summary of TEAEs potentially pertaining to drug withdrawal during the Treatment Period, as defined in Appendix 1, will be summarized by SOC and PT for the Safety Analysis Set.

Additionally, A summary table of Adverse Events potentially pertaining to drug withdrawal during the Safety Follow-up Period will be used to tabulate AEs related to drug withdrawal symptoms in the Safety Follow-Up period after EOS/ET visit, if any.

12.1.6 Potentially Pertaining to Injection Site Reactions

A summary of TEAEs potentially pertaining to injection site reactions, as defined in Appendix 1, will be summarized by SOC and PT for the Safety Analysis Set.

12.1.7 Hepatic Disorders Topic of Special Interest

A summary of TEAEs potentially related to hepatic disorders, as defined in Appendix 1, will be summarized by SOC and PT for the Safety Analysis Set.

12.1.8 Central Nervous System Depression Topic of Special Interest

A summary of TEAEs related to Central Nervous System Depression, as defined in Appendix 1, will be summarized by SOC and PT for the Safety Analysis Set.

12.1.9 Respiratory Depression Topic of Special Interest

A summary of TEAEs related to respiratory depression, as defined in Appendix 1, will be summarized by SOC and PT for the Safety Analysis Set.

12.1.10 Acute Pancreatitis Topic of Special Interest

A summary of TEAEs related to acute pancreatitis as defined in Appendix 1, will be summarized by SOC and PT for the Safety Analysis Set.

12.1.11 Orthostatic Hypotension Topic of Special Interest

A summary of TEAEs related to orthostatic hypotension, as defined in Appendix 1, will be summarized by SOC and PT for the Safety Analysis Set.

12.1.12 Psychiatry History Topic of Special Interest

A summary of TEAEs regarding psychiatry history, as defined in Appendix 1, will be summarized by SOC and PT for the Safety Analysis Set.

12.2 CLINICAL LABORATORY PARAMETERS

Laboratory data will be reported using International System (SI) units (and using original units for some parameters if necessary) 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). All laboratory assessments include a baseline summary as defined in Section 20.2 unless otherwise indicated. Hematology chemistry and urinalysis data will be summarized by displaying shifts from baseline value to EOS/ET visit. All laboratory assessments will be listed by panel with the corresponding normal ranges for each parameter. Screening laboratory tests will also be listed.

The peak total bilirubin [x ULN] vs. peak aspartate aminotransferase (or peak alanine aminotransferase) [x ULN] on a log/log scale during the Treatment Period will be plotted in the Safety Analysis Set. And the box plot to access clinical liver safety data by maximum change from baseline during the Treatment Period will be plotted for lab tests ALT, AST and total bilirubin.

Summary of potential hepatotoxicity for serum chemistry by type of criterion (shown in Table 5) and by analysis visit and at any time post baseline will be tabulated for the Safety Analysis Set. For "Any time post baseline", a subject will be classified to their highest/worst applicable toxicity grade per criterion, among the post baseline visits including unscheduled visits, and be counted only once in the category corresponding to the worst grade. For subjects who met the criteria for potential hepatotoxicity (any time post baseline), their test results for ALT, AST, TBIL, ALP during study (i.e., at all scheduled and unscheduled visit) will be provided in a listing.

Table 5: Criteria for Potential Hepatotoxicity Laboratory Value

Criteria
ALT > 3 x ULN to < 5 x ULN
ALT ≥ 5 x ULN to < 8 x ULN
ALT ≥ 8 x ULN
AST > 3 x ULN to < 5 x ULN
AST ≥ 5 x ULN to < 8 x ULN
AST ≥ 8 x ULN
ALT & AST > 3 x ULN to < 5 x ULN
ALT & AST ≥ 5 x ULN to < 8 x ULN
ALT & AST ≥ 8 x ULN
TBIL > 2 x ULN to < 5 x ULN
TBIL ≥ 5 x ULN
HYs Law: (all must be met to meet Potential Hy's law)
ALT or AST > 3 x ULN
TBIL > 2 x ULN
ULN < Alkaline phosphatase (ALP) < 2xULN

12.2.1 Hematology

Parameters include hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count (available at EOS/ET only), red blood cell count and white blood cell count with differential. Visits include Screening (or EOS Visit RB-US-13-0003) and Day 169 Week 25 (EOS INDV-6000-301) /ET visit.

12.2.2 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, lactate dehydrogenase, lipase, low-density lipoprotein, magnesium, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides and uric acid. Visits include EOS Visit RB-US-13-0003 and Day 169 Week 25 (EOS INDV-6000-301)/ET visit.

12.2.3 Urinalysis

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

Microscopic examination of sediment will be performed only if the results of the urinalysis evaluation are positive. Microscopic examination also includes but not limited to WBC count, RBC count, casts, and crystals. The microscopic results will be listed only.

12.3 VITAL SIGNS

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

Listings/tables of all vital sign assessments will be provided for the following groups:

- Supine blood pressure systolic, Supine blood pressure diastolic, Pulse rate, Oral temperature, and Respiratory rate, Pulse Oximetry;
- Body weight, BMI, Hip Circumference, Waist Circumference and Waist-to-hip ratio.

12.4 OTHER SAFETY PARAMETERS

12.4.1 Suicidality

A listing of all results will be presented for all subjects for all visits.

Table summaries will be run twice with two different baseline definitions:

- "Baseline Lifetime" will use the answers for suicidality (lifetime) in the screening/baseline questionnaire.

- "Baseline 6 months" will use the answers for suicidality (in the past 6 months) in the screening/baseline questionnaire.

<u>Suicidal Ideation Severity Scoring</u>

The suicidal ideation score ranges from 0 to 5 and depends on the answers to the suicidal ideation portion of the C-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 none of these questions are YES, then the suicidal ideation score is 0.

Suicidal Ideation Intensity Scoring

The suicidal ideation intensity score 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 behavior score ranges from 0 to 5 and depends on the answers to the suicidal behavior portion of the C-SSRS. The score is the maximum suicidal behavior 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 none of these questions are YES and the subject does not have an AE with a preferred term of completed suicide, then the suicidal behavior score is 0.

Suicidal ideation and suicidal behavior responses (Yes/No) will be summarized by analysis visit using counts and percentages in the Safety Analysis Set. Shift tables to demonstrate changes in C-SSRS categories and changes in suicidal ideation and behavior scores from baseline during the Treatment Period will be presented. CSSRS 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.

12.4.2 Local Injection Site Evaluation

The local injection site will be evaluated for potential reaction and evidence of any attempts by the subject to remove RBP-6000 following a previous injection. A summary table and a listing will be provided. Attempted removal results will be summarized by percentage of subjects with attempted removal in each dose received at each visit.

12.4.3 Local Injection Site Tolerability

Local injection site tolerability as assessed by the Injection Site Grading scale will be summarized and plotted over time by category (pain, tenderness, erythema/redness, induration, and swelling) and severity using frequency counts and percentages. Local injection site tolerability will be assigned a severity grade, including none (grade 0), mild (grade 1), moderate (grade 2), severe (grade 3), or potentially life threatening (grade 4) utilizing the 5-point Injection Site Grading Scale. A listing will be provided.

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

12.4.4 Injection Site Pain

Injection Site Pain VAS scores will be summarized over time during the Treatment Period. And the maximum score during the Treatment Period will be calculated and tabulated. The burning/stinging categorical variable (Yes/No) will be summarized by percentage of responses in each dose received at each time point.

The percentage of subjects who reported injection site reaction (Yes) at each injection visit in the Safety Analysis Set. Mean value of local injection site VAS pain scores will also be plotted at each injection.

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

12.4.5 Other Safety Variables

NA.

12.5 INDEPENDENT DRUG COUNSELING/BEHAVIOURAL THERAPY

A listing for whether independent drug counseling (IDC) was completed per subject visit will be provided.

13.0 POOLED ANALYSES

No pooled analyses will be conducted in this trial.

14.0 SUBGROUP ANALYSES

No subgroup analyses will be conducted in this trial.

15.0 HEALTH OUTCOME ANALYSES

No health outcome assessments were performed in this study.

16.0 PLASMA CONCENTRATION ANALYSES

No plasma concentration samples were collected in this study.

17.0 INTERIM ANALYSIS

No Interim analysis was performed for this study

18.0 DETERMINATION OF SAMPLE SIZE

This study is designed to provide ongoing treatment with RBP-6000 and to assess the safety monitoring for subjects who complete the RB-US-13-0003 study and for whom a new treatment venue has not been identified or arranged. Approximately 300 subjects who completed Study RB-US-13-0003 will be enrolled into this study.

19.0 COMPUTER METHODS

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

20.0 DATA HANDLING CONVENTIONS

20.1 REFERENCE DATES AND ANALYSIS PERIODS

There are two analysis periods in this study:

- Treatment Period (TP)
- Safety Follow-Up Period (SFU).

Treatment Period starts from Treatment Start Date and ends at Treatment End Date. Treatment Start Date (or Day 1) for a subject is the date of the first injection. Treatment End Date for a subject is the maximum of the date of the end-of-study/ Early Termination (EOS/ET) visit and the date of last injection + 28.

Safety Follow-Up Period starts from Safety Follow-Up Start Date and ends at Safety Follow-Up End Date, which are defined for all subject who have assessments in the Follow-Up period.

Safety Follow-Up Start Date for a subject is Treatment End Date +1.

Safety Follow-Up End Date for a subject is defined as the date of visit at Week 29 or unscheduled visit after the Treatment End Date (defined as above) for AE/concomitant medication reporting or lab/vital signs assessment, whichever comes later. That is, Follow-up end date is max (Follow-up Start Date, date of visit at Week 29, last unscheduled visit after the Treatment End Date to report AE/concomitant medication or to do lab/vital signs assessment, if available).

Any records collected prior to first injection date/time will be considered as Screening records. And any records collected after the Treatment End Date will be considered as Safety Follow-up records.

20.2 ANALYSIS VISITS AND OTHER DEFINITIONS

All data will be presented in listings (including unscheduled visits), however only per-protocol visits will be summarized in tables and figures. Unscheduled and scheduled assessments will be utilized in the summaries for “at any time”.

For lab values, body weight, BMI, waist circumference, hip circumference and waist-to-hip ratio, Early Termination and End-of-study results will be reported with the EOS/ET visit.

For all other assessments, occurring at the ET visit, will be mapped to the next per-protocol visit (or time point), that has not already been completed by the subject. A ET visit must not be mapped to a visit that a subject has already completed.

The closest assessment value on or before Treatment Start Date/Time will be assigned as Baseline value and then be labeled as 'Baseline' in visit window, and for assessment prior to Treatment Start Date/Time, if exists, will be labeled as 'EOS 0003' or 'Screening' per its collecting time and per SOE definition.

For subjects who have one visit-based assessment in the Safety Follow-up (SFU) period, the period of the visit will be labeled as 'Safety Follow-Up Week 29'.

Other Definitions:

Subgroups

Sex

- Male
- Female

Age Categories

- ≥ 18 to < 30
- ≥ 30 to < 45
- ≥ 45 to < 60
- ≥ 60
- ≥ 65

Race

- White
- Non-White

Baseline BMI Categories

- Under weight: 0 to < 18.5 kg/m^2
- Normal: ≥ 18.5 kg/m^2 and < 25 kg/m^2
- Over weight: ≥ 25 kg/m^2 and < 30 kg/m^2
- Obese: ≥ 30 kg/m^2

20.3 DERIVED EFFICACY VARIABLES

Not applicable.

20.4 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

See reference rules on unscheduled assessments in Section 20.2. Unscheduled assessments will be utilized in analyses "at any time" and will be listed in listings.

If there are more one assessments on one parameter at scheduled visits, the last assessment will be used for visit-based table/figure summaries.

20.5 MISSING DATE OF INVESTIGATIONAL PRODUCT

When the date of the last injection of RBP-6000 during the Treatment Period is missing for a subject in the Safety Population, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last available dosing record date will be used as the last dose date.

20.6 MISSING SEVERITY AND RELATIONSHIP TO STUDY DRUG IN ADVERSE EVENTS

If the severity is missing for an AE started on or after the date of the first dose of the investigational product, then a severity of "Severe" will be assigned.

If the relationship is missing for an AE started on or after the date of the first dose of the investigational product, then a relationship of "Related" will be assigned.

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

20.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

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

Missing day and month

- If the year is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.

- If the year is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.

- If the year is after the year of the date of the first dose of investigational product, then January 1 will be assigned to the missing fields.

Missing month only

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

Missing day only

- If the month and year are the same as the month and year of the date of the first dose of investigational product, then the day of the first dose of investigational product will be assigned to the missing day.

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

If the stop date is after the date of the first dose of investigational product, the date of the first dose of investigational product will be assigned to the missing start date

If the stop date is before the date of the first dose of investigational product, the stop date will be assigned to the missing start date

20.8 MISSING DATE INFORMATION FOR CONCOMITANT MEDICATIONS

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

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose 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 investigational product, then December 31 will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then January 1 will be assigned to the missing fields.

Missing month only

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

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the first dose will be assigned to the missing day.

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

Incomplete Stop Date

Missing day and month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of investigational product, then the day and month of the date of the last dose 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 investigational product, then December 31 will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then January 1 will be assigned to the missing fields.

Missing month only

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

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the last dose will be assigned to the missing day.

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

20.9 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS AND OTHER LABORATORY IMPUTATION RULES

- If a reported value of a clinical laboratory parameter cannot be used in a statistical summary table due, for example, to the fact that a character string is reported for a parameter of the numerical type, a coded value needs to be appropriately determined and used in the statistical analyses. Value of X+0.0001 will be used to impute ">X" character value and X-0.0001 will be used to impute "<X". That is, if X equal to 60, 60.0001 will be used to impute character value of ">60" and 59.999 will be used to impute "<60". However, the actual values as reported in the database may be presented in data listings.

- Due to the fact that screening lab records were rolled-over from RB-US-13-0003, whose LDH, total bilirubin and AST records have lower limits and HDL-C records have upper limit as opposed to at visits after first injection only having one-sided upper limits for parameters LDH, total bilirubin and AST and one-sided lower limit for HDL-C, lab classsification values (i.e., Low, normal and high) for parameters LDH, total bilirubin and AST and HDL-C at screening and from RB-US-13-0003 should be imputed so that shift tables can be tabulated. The imputation rules are as follows:

    - For screening records (ie, rolled-over from RB-US-13-0003) of parameters LDH, total bilirubin and AST, lower limits will be imputed as 0. The lab character values of "Low" and "Normal" will be collapsed to be "Normal".

    - For screening records (ie, rolled-over from RB-US-13-0003) of HDL-C, upper limit will be imputed as blank. The lab character values of "Normal" and "High" will be collapsed to be "Normal".

- GGT assessments at Screening have categories of normal and high but have three categories of low, normal and high post-baseline. Then for GGT post-baseline assessments, low and normal will be collapsed to normal.

20.10 C-SSRS DATA IMPUTATION

In the Suicidal Behavior section, when the answer to the question "Have you made a suicide attemp" is NO, then the "Total # of Attempts" should be 0. In our clincial database, we have both 0 and Blank present. In the analysis dataset, under this scenario, Blank for Total # of Attempts will be imputed as 0.

21.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

No changes have been made to analyses specified in protocol.

22.0 REFERENCES

Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER)

23.0 APPENDIX

23.1 APPENDIX 1: LIST OF PREFERRED TERMS FROM STANDARD MEDDRA QUERIES FOR ADVERSE EVENTS OF SPECIAL INTEREST

LIST OF PREFERRED TERMS FOR PSYCHIATRIC HISTORY

Adjustment disorder with anxiety	Cyclothymic disorder
Adjustment disorder with depressed mood	Bipolar disorder
Adjustment disorder with disturbance of conduct	Hypomania
Adjustment disorder with mixed anxiety and depressed mood	Mania
Adjustment disorder with mixed disturbance of emotion and conduct	Blunted affect
Grief reaction	Constricted affect
Adjustment disorder	Flat affect
Agitation	Inappropriate affect
Agitation neonatal	Affect lability
Anticipatory anxiety	Affective ambivalence
Anxiety	Anger
Nervousness	Dysphoria
Stress	Emotional disorder
Tension	Emotional poverty
Activation syndrome	Euphoric mood
Acute stress disorder	Irritability
Post-traumatic stress disorder	Moaning
Postpartum stress disorder	Mood altered
Burnout syndrome	Emotional distress
Anniversary reaction	Neuroleptic-induced deficit syndrome
Acrophobia	Alexithymia
Agoraphobia	Frustration tolerance decreased
Animal phobia	Mood swings
Claustrophobia	Affective disorder
Fear	Apathy
Fear of animals	Listless
Fear of closed spaces	Mood disorder due to a general medical condition
Fear of disease	Seasonal affective disorder
Fear of open spaces	Boredom

Fear of weight gain	Laziness
Performance fear	Substance-induced mood disorder
Phobia	Aggression
Phobia of exams	Antisocial behaviour
Phobia of flying	Asocial behaviour
Phobic avoidance	Attention-seeking behaviour
Social anxiety disorder	Belligerence
Social fear	Disinhibition
Fear of falling	Grandiosity
Dysmorphophobia	Hostility
Ochlophobia	Indifference
Phagophobia	Inferiority complex
Fear of crowded places	Negativism
Fear of eating	Paranoia
Arachnophobia	Personality change
Hydrophobia	Social avoidant behaviour
Phonophobia	Soliloquy
Phobia of driving	Suspiciousness
Noctiphobia	Violence-related symptom
Nocturnal fear	Homicidal ideation
Osmophobia	Impatience
Nosophobia	Disturbance in social behaviour
Photaugiaphobia	Aversion
Thanatophobia	Suggestibility
Fear of death	Stubbornness
Fear of pregnancy	Pseudologia
Haphephobia	Overconfidence
Paruresis	Egocentrism
Pharmacophobia	Defiant behaviour
Emetophobia	Personality disorder
Autophobia	Pithiatism
Haemophobia	Self esteem decreased
Fear of injection	Self esteem inflated
Thermophobia	Avoidant personality disorder
Algophobia	Dependent personality disorder
Limited symptom panic attack	Obsessive-compulsive personality disorder
Panic attack	Antisocial personality disorder
Panic disorder	Borderline personality disorder
Panic reaction	Histrionic personality disorder

Compulsions	Narcissistic personality disorder
Obsessive thoughts	Psychopathic personality
Obsessive-compulsive disorder	Paranoid personality disorder
Trichotillomania	Schizoid personality disorder
Body dysmorphic disorder	Schizotypal personality disorder
Obsessive rumination	Breath holding
Dermatillomania	Staring
Compulsive lip biting	Regressive behaviour
Nail picking	Abnormal behaviour
Compulsive shopping	Sexually inappropriate behaviour
Compulsive hoarding	Behaviour disorder due to a general medical condition
Compulsive handwashing	Scatolia
Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection	Neglect of personal appearance
Trichotemnomania	Trance
Compulsive cheek biting	Hypervigilance
Obsessive need for symmetry	Abulia
Obsessive-compulsive symptom	Psychiatric symptom
Anxiety disorder due to a general medical condition	Psychiatric decompensation
Generalised anxiety disorder	Decreased eye contact
Neurosis	Psychological trauma
Postpartum neurosis	Helplessness
Selective mutism	Personality change due to a general medical condition
Separation anxiety disorder	Mental disorder due to a general medical condition
Anxiety disorder	Neuropsychiatric syndrome
Catatonia	Psychological factor affecting medical condition
Restlessness	Mental status changes
Automatism	Dyslogia
Automatism epileptic	Mental disorder
Automatism, command	Emotional disorder of childhood
Bruxism	Neurotic disorder of childhood
Echolalia	Personality disorder of childhood
Echopraxia	Reactive attachment disorder of infancy or early childhood
Head banging	School refusal
Posturing	Disinhibited social engagement disorder of childhood
Stereotypy	Encopresis
Waxy flexibility	Enuresis

Tic	Alcohol abuse
Chronic tic disorder	Alcohol problem
Complex tic	Alcoholic hangover
Provisional tic disorder	Alcoholism
Secondary tic	Dependence
Attention deficit/hyperactivity disorder	Drug abuse
Atypical attention deficit syndrome	Drug dependence
Oppositional defiant disorder	Drug dependence, antepartum
Conduct disorder	Drug dependence, postpartum
Disruptive mood dysregulation disorder	Tobacco abuse
Change in sustained attention	Withdrawal syndrome
Distractibility	Alcohol withdrawal syndrome
Daydreaming	Nicotine dependence
Executive dysfunction	Tobacco withdrawal symptoms
Vascular cognitive impairment	Neonatal complications of substance abuse
Mental fatigue	Substance abuse
Learning disability	Dopamine dysregulation syndrome
Reading disorder	Binge drinking
Learning disorder	Substance dependence
Mutism	Gambling disorder
Communication disorder	Brief psychotic disorder, with postpartum onset
Speech sound disorder	Brief psychotic disorder with marked stressors
Clang associations	Transient psychosis
Logorrhoea	Brief psychotic disorder without marked stressors
Neologism	Alice in wonderland syndrome
Verbigeration	Delusional disorder, erotomanic type
Taciturnity	Delusional disorder, grandiose type
Disorganised speech	Delusional disorder, jealous type
Coprolalia	Delusional disorder, mixed type
Lack of spontaneous speech	Delusional disorder, somatic type
Poverty of speech	Delusional disorder, unspecified type
Pressure of speech	Delusional disorder, persecutory type
Screaming	Acute psychosis
Dysphemia	Alcoholic psychosis
Confusional state	Psychotic behaviour
Disorientation	Senile psychosis
Delirium	Shared psychotic disorder
Delirium tremens	Reactive psychosis
Delirium febrile	Epileptic psychosis

Post-traumatic amnestic disorder	Childhood psychosis
Korsakoff's syndrome	Psychotic disorder
Paramnesia	Psychotic disorder due to a general medical condition
Pseudodementia	Hysterical psychosis
Behavioural and psychiatric symptoms of dementia	Postictal psychosis
Agitated depression	Substance-induced psychotic disorder
Depression	Rebound psychosis
Depression suicidal	Parkinson's disease psychosis
Postpartum depression	Schizoaffective disorder
Major depression	Schizophreniform disorder
Menopausal depression	Schizoaffective disorder bipolar type
Childhood depression	Schizoaffective disorder depressive type
Post stroke depression	Schizophrenia
Postictal depression	Anorgasmia
Persistent depressive disorder	Female orgasmic disorder
Anhedonia	Male orgasmic disorder
Decreased interest	Orgasm abnormal
Depressed mood	Premature ejaculation
Feeling of despair	Orgasmic sensation decreased
Feelings of worthlessness	Psychosexual disorder
Morose	Sex dysphoria
Psychomotor retardation	Sexual inhibition
Tearfulness	Psychogenic erectile dysfunction
Feeling guilty	Disturbance in sexual arousal
Depressive symptom	Excessive masturbation
Negative thoughts	Libido decreased
Sense of a foreshortened future	Libido increased
Autism spectrum disorder	Loss of libido
Neurodevelopmental disorder	Sexual aversion disorder
Dissociation	Excessive sexual fantasies
Dissociative amnesia	Libido disorder
Dissociative disorder	Hypersexuality
Dissociative identity disorder	Compulsive sexual behaviour
Depersonalisation/derealisation disorder	Genito-pelvic pain/penetration disorder
Delusion	Exhibitionism
Delusion of grandeur	Fetishism
Delusion of reference	Frotteurism
Delusion of replacement	Masochism

Erotomanic delusion	Paedophilia
Jealous delusion	Paraphilia
Persecutory delusion	Sadism
Somatic delusion	Transvestism
Thought insertion	Voyeurism
Thought withdrawal	Initial insomnia
Thought broadcasting	Insomnia
Cotard's syndrome	Middle insomnia
Depressive delusion	Hyposomnia
Mixed delusion	Terminal insomnia
Deja vu	Behavioural insomnia of childhood
Delusional perception	Breathing-related sleep disorder
Derealisation	Dyssomnia
Flashback	Hypnagogic hallucination
Hallucination	Hypnopompic hallucination
Hallucination, auditory	Sleep attacks
Hallucination, gustatory	Abnormal dreams
Hallucination, olfactory	Nightmare
Hallucination, tactile	Rapid eye movements sleep abnormal
Hallucination, visual	Sleep talking
Hallucinations, mixed	Sleep terror
Illusion	Somnambulism
Jamais vu	Abnormal sleep-related event
Somatic hallucination	Parasomnia
Hallucination, synaesthetic	Loss of dreaming
Paroxysmal perceptual alteration	Sleep-related eating disorder
Time perception altered	Sleep sex
Autoscopy	Sleep inertia
Circumstantiality	Confusional arousal
Confabulation	Rapid eye movement sleep behaviour disorder
Derailment	Sleep disorder due to general medical condition, hypersomnia type
Flight of ideas	Sleep disorder due to general medical condition, insomnia type
Ideas of reference	Sleep disorder due to general medical condition, mixed type
Illogical thinking	Sleep disorder due to general medical condition, parasomnia type
Loose associations	Sleep disorder due to a general medical condition
Magical thinking	Sleep disorder

Perseveration	Hypersomnia-bulimia syndrome
Poverty of thought content	Sopor
Tangentiality	Hypersomnia related to another mental condition
Thinking abnormal	Insomnia related to another mental condition
Thought blocking	Completed suicide
Bradyphrenia	Intentional self-injury
Morbid thoughts	Suicidal ideation
Intellectualisation	Suicide attempt
Tachyphrenia	Self-injurious ideation
Impaired reasoning	Self injurious behaviour
Paralogism	Suicidal behaviour
Pathological doubt	Suicide threat
Intrusive thoughts	Compensation neurosis
Purging	Munchausen's syndrome
Self-induced vomiting	Factitious disorder
Eating disorder symptom	Conversion disorder
Anorexia and bulimia syndrome	Polydipsia psychogenic
Anorexia nervosa	Psychogenic dysuria
Binge eating	Torticollis psychogenic
Bulimia nervosa	Vomiting psychogenic
Eating disorder	Psychosomatic disease
Merycism	Pseudoneurologic symptom
Pica	Psychogenic seizure
Food aversion	Psychogenic movement disorder
Selective eating disorder	Psychogenic tremor
Impulsive behaviour	Psychogenic respiratory distress
Intermittent explosive disorder	Somatoform genitourinary disorder
Kleptomania	Somatic symptom disorder
Poriomania	Illness anxiety disorder
Pyromania	Cardiovascular somatic symptom disorder
Onychophagia	Gastrointestinal somatic symptom disorder
Impulse-control disorder	Neurologic somatic symptom disorder
Necromania	Cutaneous somatic symptom disorder
Clinomania	Somatic symptom disorder of pregnancy
Bipolar I disorder	
Bipolar II disorder	

CUSTOMIZED 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

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	

CMQ LIST OF PREFERRED TERMS FOR CNS DEPRESSION

Mental fatigue	Hyporesponsive to stimuli
Microsleep	Benign familial neonatal convulsions
Narcolepsy	Febrile convulsion
Coma	Drug withdrawal convulsions
Impaired driving ability	Convulsion neonatal
Impaired ability to use machinery	Convulsions local
Accident	Tonic convulsion
Road traffic accident	Convulsion in childhood
Vision blurred	Clonic convulsion
Vertigo CNS origin	Acute encephalitis with refractory, repetitive partial seizures
Incoherent	Generalised tonic-clonic seizure
Disturbance in attention	Complex partial seizures

Judgement impaired	Psychomotor seizures
Mental impairment	Simple partial seizures
Borderline mental impairment	Autonomic seizure
Cognitive disorder	Atonic seizures
Altered state of consciousness	Seizure
Depressed level of consciousness	Partial seizures with secondary generalisation
Lethargy	Alcoholic seizure
Loss of consciousness	Partial seizures
Sedation	Seizure like phenomena
Somnolence	Seizure cluster
Somnolence neonatal	Change in seizure presentation
Stupor	Migraine-triggered seizure
Syncope	Psychogenic seizure
Postictal state	Seizure anoxic
Consciousness fluctuating	Post stroke seizure
Neonatal oversedation	Accidental death
Hypoglycaemic unconsciousness	Accidental overdose
Hyperglycaemic unconsciousness	Accidental exposure to product
Post-injection delirium sedation syndrome	Cerebrovascular accident
Preictal state	Dizziness
Psychogenic pseudosyncope	Dizziness exertional
Mental status changes	Dizziness postural
Mental status changes postoperative	Procedural dizziness
Slow response to stimuli	Neurotoxicity
Unresponsive to stimuli	

CMQ LIST OF PREFERRED TERMS FOR RESPIRATORY DEPRESSION/RESPIRATORY FAILURE

Acute respiratory distress syndrome	Neonatal respiratory arrest
Acute respiratory failure	Neonatal respiratory depression
Apnoea	Neonatal respiratory distress syndrome
Apnoea neonatal	Neonatal respiratory failure
Infantile apnoea	Respiratory arrest
Apnoeic attack	Respiratory depression
Bradypnoea	Respiratory depth decreased

Breath sounds absent	Respiratory distress
Cardio-respiratory distress	Respiratory failure
Central-alveolar hypoventilation	Respiratory paralysis
Chronic respiratory failure	Respiratory rate decreased
Hypopnoea	Severe acute respiratory syndrome
Hypoventilation	Cardio-respiratory arrest
Hypoventilation neonatal	Cardio-respiratory arrest neonatal
Lung hypoinflation	Cardiopulmonary failure
Meconium aspiration syndrome	

CMQ LIST OF PREFERRED TERMS FOR ORTHOSTATIC HYPOTENSION

Orthostatic hypotension	Syncope
Vision blurred	Presyncope
Dizziness	Diastolic hypotension
Dizziness exertional	Hypotension
Dizziness postural	

CMQ LIST OF PREFERRED TERMS FOR WITHDRAWAL SYMPTOMS

Agitation	Malaise
Anxiety	Muscle spasms
Arthralgia	Muscle twitching
Bone pain	Myalgia
Chills	Mydriasis
Decreased appetite	Nausea
Depression	Piloerection
Diarrhoea	Pruritus
Dizziness	Psychomotor hyperactivity
Drug dependence	Pyrexia
Flushing	Respiratory rate increased
Heart rate increased	Restlessness
Hyperhidrosis	Rhinitis
Hypertension	Rhinorrhoea
Hypervigilance	Sneezing
Influenza like illness	Tachycardia

Insomnia	Tremor
Irritability	Vomiting
Lacrimal disorder	Yawning
Lacrimation increased	Drug withdrawal symptoms
Muscle strain	

CMQ LIST OF PREFERRED TERMS FOR ACUTE PANCREATITIS

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

23.2 APPENDIX 2: LIST OF CYP3A4 INHIBITOR MEDICATIONS

Generic/Brand Name	Category	Generic/Brand Name	Category
Alprazolam	weak	isoniazid	weak
Amiodarone	weak	istradefylline	weak
Amlodipine	weak	Itraconazole	strong
Amprenavir	moderate	ivacaftor	weak
Aprepitant	moderate	Ketoconazole	strong
Atazanavir	moderate	lapatinib	weak
Atorvastatin	weak	lomitapide	weak
Bicalutamide	weak	lopinavir	strong

boceprevir	strong	Mestranol	weak
Chloramphenicol	unclassified	Metronidazole	unclassified
chlorzoxazone	weak	Mibefradil	strong
cilostazol	weak	Miconazole	unclassified
Cimetidine	moderate	Mifepristone	unclassified
Ciprofloxacin	moderate	Nefazodone	strong
Clarithromycin	strong	Nelfinavir	strong
Clotrimazole	moderate	Nicardipine	unclassified
cobicistat	strong	nilotinib	weak
conivaptan	strong	Norfloxacin	unclassified
crizotinib	moderate	Norfluoxetine	unclassified
Cyclosporine	moderate	ombitasvir	strong
danoprevir	strong	paritaprevir	strong
darunavir	moderate	pazopanib	weak
dasabuvir	strong	posaconazole	strong
Delavirdine	strong	Progestogen	weak
Diethyldithiocarbamate	unclassified	Propofol	unclassified
Diltiazem	strong	Quinine	unclassified
dronedarone	moderate	Ranitidine	weak
elvitegravir	strong	ranolazine	weak
Erythromycin	moderate	Ritonavir	strong
estradiol	weak	Saquinavir	strong
ethinyl	weak	Sertraline	unclassified
Fluconazole	moderate	Starfruit	unclassified
Fluoxetine	weak	tacrolimus	weak
Fluvoxamine	moderate	Telaprevir	strong
fosamprenavir	moderate	Telithromycin	strong
fosaprepitant	weak	ticagrelor	weak
Gestodene	weak	tipranavir	strong
ginkgo	weak	tofisopam	moderate
goldenseal	weak	troleandomycin	strong
grapefruit	strong	Verapamil	moderate
idelalisib	strong	voriconazole	strong

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