Cover Page

BPL-003-203 Statistical Analysis Plan

Clinical Trial Protocol Title: An Open-Label, Phase 2a Single Dose Study in Patients With Alcohol Use Disorder

NCT Number: NCT05674929

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Statistical Analysis Plan

Clinical trial protocol title:	An Open-Label, Phase 2a Single Dose Study in Patients With Alcohol Use Disorder
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1 List of abbreviations

5-MeO-DMT	5-methoxy-N,N-dimethyltryptamine
5-MIAA	5-methoxyindolacetic acid
ACQ	Alcohol Craving Questionnaire
AESS	Adverse events of special situations
AESI	Adverse events of special interest
AE	Adverse event
AUD	Alcohol use disorder
BLQ	Below the limit of quantification
BP	Blood pressure
CDT	Carbohydrate deficient transferrin
CGIS	Clinical Global Impression Severity
CI	Confidence interval
CIWA-Ar	Clinical Institute Withdrawal Assessment
CRF	Case report form
CSR	Clinical study report
C-SSR	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
EDI	Ego Dissolution Inventory
EQ-5D-5L	5-level EuroQol-5 Dimension
EtG	Ethylglucuronide
HDD	Heavy drinking days
HR	Heart rate
ICH	International Conference on Harmonization
ITT	Intent-to-treat
MADRS	Montgomery–Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MEQ-30	Mystical Experience Questionnaire
MHRA	Medicines and Healthcare products Regulatory Agency
N	Number of patients
n	Number of observations used in analysis
PAD	Percentage of Abstinent days
PCI	Potential clinical importance
PD	Pharmacodynamic(s)
PDD	Percentage of drinking days
PGIC	Patient Global Impression of Change
PHDD	Percentage of heavy drinking days
PK	Pharmacokinetic(s)
PP	Per protocol
PR	Portion of the ECG from the beginning of the P wave to the beginning of the QRS complex, representing atrioventricular node function.
QOL	Quality of life
QRS	The QRS complex of the ECG reflects the rapid depolarization of the right and left ventricles.
QT	Portion of the ECG between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization.

QTc	Corrected portion of the ECG between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization.
QTcF	QTc interval with Fridericia's correction method
RDQ	Readiness for discharge questionnaire
ReAQ	Reactivation Questionnaire
RR	Portion of the ECG between consecutive R waves, representing the ventricular rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SETS	Stanford Expectations of Treatment Scale
SD	Standard deviation
SIP	Short Inventory of Problems
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event
TLFB	Timeline Follow-Back
t_{max}	Time to maximum plasma concentration
UPD	Units per day
VAS	Visual Analogue Scale
WHO	World Health Organisation

2 Signatures

The following persons have read and agreed the content of this Statistical Analysis Plan:

Steven Whaley Principal Statistician, HMR	Signature	Date
Dr Mathieu Seynaeve Senior Medical Director and Head of Psychotherapy, Beckley Psytech Ltd	Signature	Date
Claire Roberts VP & Head of Clinical Development, Beckley Psytech Ltd.	Signature	Date

3 Introduction

This statistical analysis plan (SAP) is based on the current trial protocol (Version 7.0, dated 29 August 2024). Where statistical methods differ substantially between this SAP and the protocol, that will be identified in this document.

This SAP describes the datasets and the statistical methods to be used for the reporting and analysis of all data collected during the trial, except:

- Qualitative interview data (description of the BPL-003 subjective experience), psychological change measures and semi-structured interviews which will be analysed and reported separately
- Treatment model, feedback from therapists which will be reported separately

If a future protocol amendment necessitates a substantial change to the statistical analysis of the trial data, this SAP will be amended accordingly. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, those unplanned analyses will not be described in an amended SAP, but they will be identified in the integrated clinical study report (CSR). Any deviations from this SAP will be documented in the CSR.

This SAP has been written in consideration of the following guidelines:

- International Conference on Harmonization (ICH) E9, Guidance for Industry: Statistical Principles for Clinical Trials (ICH E9 1998[1]); and
- ICH E3, Guidance for Industry: Structure and Content of Clinical Study Reports (ICH E3 1995)[2].

Statistical analysis will be done using SAS ® 9.4 or higher on a Windows PC.

4 Study objective(s) and endpoint(s)

4.1 Study objective(s)

4.1.1 Primary objective

- To assess the safety and tolerability of single intranasal dose of BPL-003 (5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT)) in patients with alcohol use disorder (AUD)

4.1.2 Secondary objective(s)

- To assess the pharmacodynamics (PD; including psychological effects) of single intranasal doses of BPL-003 in patients with AUD
- To assess the feasibility of the treatment model for BPL-003 combined with relapse prevention psychotherapy in patients with AUD

4.1.3 Exploratory objective(s)

- To explore the effects of a single intranasal dose of BPL-003 combined with relapse prevention psychotherapy in patients with AUD on alcohol use and related symptoms
- To explore the effects of BPL-003 combined with relapse prevention psychotherapy on health-related quality of life (QOL) in patients with AUD
- To explore exposure levels after a single intranasal dose of BPL-003 in patients with AUD
- To assess the correlation of PD effects with alcohol use and related symptoms
- To determine participant expectations of treatment outcome

4.2 Study endpoint(s)

4.2.1 Primary endpoint(s)

Safety Endpoints:

- Percentage of patients with treatment-emergent adverse events (TEAEs)
- Percentage of patients with clinically significant postdose abnormal laboratory tests
- Percentage of patients with clinically significant abnormal postdose vital sign measurements (Heart rate (HR), Blood Pressure (BP), and body temperature)
- Percentage of patients with postdose suicidal ideation as determined by the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Change in C-SSRS score compared to Baseline at Days 7 and 84
- Readiness for discharge questionnaire
- Measure the frequency, emotional valence and functional impact of any re-activation events in the study through the Reactivation Questionnaire (ReAQ)

4.2.2 Secondary endpoint(s)

Pharmacodynamic Endpoints:

- The effects of BPL-003 as determined by the Mystical Experience Questionnaire (MEQ-30) and Ego Dissolution Inventory (EDI)
- Percentage (%) of patients experiencing a complete mystical experience, as assessed by the MEQ-30 on Day 0
- Description of the BPL-003 subjective experience data (from the qualitative interview)#
- Psychological change as measured with a questionnaire and semi-structured interview

Treatment Model:#

- Treatment model, feedback from therapists on
  - Frequency and duration of psychotherapy sessions
  - Implementation of therapy manuals
- Overall therapy model

4.2.3 Exploratory endpoint(s)

Pharmakokinetic:

- Blood samples to determine 5-MeO-DMT and its metabolites (including bufotenine) plasma concentrations will be taken after dosing on Day 0.

Drinking Cravings and withdrawal:

- Change in alcohol craving as measured by Alcohol Craving Questionnaire (ACQ) at Days 1, 7, 28, 56, and 84 compared to Baseline (pre-dose Day 0)
- Alcohol cravings as measured by Craving Visual Analogue Scale (VAS)
- Alcohol withdrawal symptoms as measured by Clinical Institute Withdrawal Assessment (CIWA-Ar)

Alcohol Use:

- Using the Timeline Follow-Back (TLFB) interview, the following parameters of alcohol use in the 90 days before dosing and endpoint will be recorded:
    - Longest duration (days) of continuous abstinence
    - Maximum number of standard units of alcohol consumed on any one day
    - Number of Heavy Drinking Days (HDD)
    - Percentage of Heavy Drinking Days (PHDD) in 85d prior D-3 (or start of detox) vs PHDD post-dosing measured on d14, d28, d56, d84
    - Percentage of drinking days (PDD) in 85d prior D-3 (or start of detox) vs PDD post-dosing measured on d14, d28, d56, d84.
    - Mean Units per day (UPD): In 85d prior D-3 (or start of detox) vs UPD post-dosing measured on d14, d28, d56, d84.
    - Abstinence: Percentage of Abstinent days (PAD) in 85d prior D-3 (or start of detox) vs PAD on d14, d28, d56, d84 (with biomarker verification).
    - Number of days after BPL-003 dosing to first drink
    - Number of days after BPL-003 dosing to first HDD (defined by UK government as >=7 units a day for a woman and >=9 units per day for a man)
    - Average number of standard units of alcohol consumed per week in 85d prior D-3 (or start of detox) vs post-dosing measured on d14, d28, d56, d84 (and reported referencing UK risk levels)
- Consequences of alcohol use as measured by Short Inventory of Problems (SIP)
- Biomarkers:
    - Alcohol use as measured by Ethylglucuronide (EtG) in urine at Days 1, 28, 56, 84 compared to Screening
    - Alcohol use as measured by carbohydrate deficient transferrin (CDT) in blood at Days 28 & 84 compared to Screening

Pharmacodynamic

- The correlation of the occurrence of a "complete mystical experience" and "ego dissolution", measured by the MEQ-30 and EDI, with improvement in alcohol use and craving (measured by ACQ, TLFB, EtG, CDT)

Wellbeing:

- Change in Montgomery–Asberg Depression Rating Scale (MADRS) at Days 28, 56, and 84 compared to Baseline
- Change in Clinical Global Impression Severity (CGIS) at Days 1, 28, 56, and 84 compared to Baseline
- Patient Global Impression of Change (PGIC) at Days 1, 28, 56, and 84
- Change in 5-level EuroQol-5 Dimension (EQ-5D-5L) at Days 28 and 84 compared to Baseline

Expectation:

- Assess positive and negative expectations as measured by Stanford Expectations of Treatment Scale (SETS)

# denotes to be reported separately

4.3 Statistical hypotheses

The trial is an exploratory one, and there are no null hypotheses to be tested.

5 Study design

An open-label, dual-centre, Phase 2a study to evaluate the safety, tolerability, and PD effects of a single intranasal dose of BPL-003 combined with relapse prevention psychotherapy to assess the treatment model and explore the potential effects on alcohol use and related symptoms. This study will assess a dry powder nasal spray formulation of 5-MeO-DMT benzoate (BPL-003). Enrolment of up to 12 patients with AUD is planned in up to 2 cohorts (Cohorts 1 and 2).

Patients will receive a single dose of 10 mg (Cohort 1) or 12 mg (Cohort 2) BPL-003. The doses selected for this study are based on a review of safety, tolerability, pharmacokinetic (PK), and PD data from the dose levels tested to date in study BPL-003-103 (a single ascending-dose study in healthy volunteers).

After completing the screening period, those patients who are confirmed as eligible will participate in a minimum of 3 preparatory psychological support sessions over approximately 2 weeks before the BPL-003 treatment session. These sessions will be conducted by a therapist with psychedelic knowledge and an AUD therapist. The last of the 3 sessions will be conducted at the clinic where the dosing will occur so that patients can become familiar with the dosing room, clinic staff and a practice run with the nasal delivery system can be completed. Baseline assessments will be completed on the BPL-003 treatment day, before BPL-003 administration.

BPL-003 will be administered on the treatment day in accordance with established safety practices for psychedelic research. A minimum of 3 integration sessions will occur over approximately 2 weeks after the treatment session, together with AUD relapse prevention psychotherapy that will guide the patient through the 12-week postdose follow-up period.

If triggered by the sponsor, a Safety Review Committee (SRC) will decide upon continuation of the study at the 10 mg dose or escalation to 12 mg. The SRC will comprise of, as a minimum, one Investigator (or delegate), the Sponsor's medical monitor, and the Chief Medical Officer (or delegate). The SRC will review, as a minimum, safety, tolerability, PK and PD data up to Day 1 from at least 3 patients dosed with 10 mg BPL-003 in Cohort 1. The dose may be escalated to 12 mg only if the safety, tolerability, PK and PD at 10 mg are deemed acceptable by the SRC. Dose decisions will be documented before further dosing. Additional SRC meetings may be scheduled as required.

The study visits and procedures are outlined below:

- **Screening:** Patients will be screened up to 14 days before their psychedelic preparation session to confirm their eligibility for the study.

- **Abstinence:** Patients will be expected to have no HDD in the 72 hours prior to dosing, and no alcohol in the last 24 hours. If breath alcohol is not zero on dosing day, patients may reschedule once if they are deemed not to have completely relapsed; however, if they fail the second time, they will be excluded from the study.

- **Psychedelic preparation visits:** Following the initial Screening Visit, all patients will participate in 3 preparatory sessions over approximately 2 weeks before being dosed (patients should not undertake preparation sessions if intoxicated (clinical judgement to be applied whether the patient is able to absorb the information and build a therapeutic alliance). The aim will be to establish a therapeutic alliance with the therapists during the preparatory sessions so that patients will be well prepared for the BPL-003 treatment session and receive ongoing AUD relapse prevention psychotherapy.

- **Psychological change measures and semi-structured interviews (optional):** if patients consent to these optional assessments they will be required to complete psychological change questionnaires at 5 visits during the study on Days –3, 1, 7, 28 and 84, and 3 semi-structured interviews with a therapist on Days 1, 28 and 84 (as detailed in the Psychological Change Study Manual).

- **Dosing visit:** After completion of the 3 preparatory sessions, patients will attend the clinic for their dosing visit. Patients will be resident at the clinic from the morning of Day 0 (dosing day) until at least 4 hours postdose. BPL-003 will be administered to patients in the designated setting, and the therapist will remain with patients while patients are in an altered state of consciousness.

- **Qualitative interview (optional):** After return to a usual state of consciousness after dosing, and provided they consent, patients will be asked to have a one-to-one guided

qualitative interview with independent researchers trained in microphenomenology methods to discuss their psychedelic experience (as detailed in the Qualitative Interview Study Manual). This will be done either face to face at the clinic or via video call. Psychometric scales will then be administered to provide quantitative measures of the patient's psychedelic experience.

All patients will have their readiness for discharge assessed every 30 minutes starting 90 minutes after dosing before discharge on the dosing day. The earliest a patient can be discharged will be 4 h after receiving the dose.

- **Follow-up (for 12 weeks postdose):**
  - **Psychedelic integration sessions:** Patients will have at least 3 integration sessions, lasting approximately 60-90 min, over the 2 weeks following their dose to discuss their experience with the therapists.
  - **Relapse prevention psychotherapy:** Patients will have weekly sessions following the dose of BPL-003 as defined in the AUD Therapy Manual (can be either face to face or remote) with an AUD therapist.

6 Schedule of events

Please refer to Table 1 of the protocol, version 7, dated 29 August 2024

7 Planned analyses

7.1 Interim analyses

No interim analyses are planned. This is an open label study and data will be reviewed on an ongoing basis by the Sponsor. In addition, data will be reviewed by the SRC before dose escalation.

7.2 Final analysis

The database will be locked once all patients have completed the study, data have been entered, and queries resolved. The final analysis will be carried out following database lock.

7.2.1 Persons responsible for analysis

Steven Whaley Statistician

8 Sample size considerations

8.1 Sample size assumptions

As this is a pilot study, no formal sample size determination is appropriate

9 Analysis populations

The following populations will be identified:

Safety population: All patients who received the dose of study drug

Intent-to-treat population (ITT) population: All patients who received the study drug and a PD measure is available.

Per protocol (PP) population: All patients who received study drug and a PD measure is available and not deemed to have an important major protocol deviations

PK concentration population: All subjects who received the study drug and for whom a pharmacokinetic sample has been analysed

The primary endpoint will be analysed using the safety population.

PD endpoints will be analysed using the ITT population. A sensitivity analysis using the PP population for Alcohol use, and MEQ-30 endpoints will be performed.

9.1 Analysis datasets

All analysis datasets will be based on observed data, except as outlined in Section 12.2.

10 Treatment comparisons

The treatment comparison of interest is active between ascending dose levels.

11 General considerations for data analyses

11.1 Data display treatment and other subgroup descriptors

The sort order for treatment groups will be study treatment in ascending dose order.

Listings of data will be sorted and displayed by treatment group, patient number, and also by date and time if applicable.

The treatment descriptions to be used on all tables and listings are:

Treatment Groups
10 mg BPL-003

11.2 Conventions for summary statistics and data displays

The minimum set of summary statistics for numeric variables will be: n, mean, standard deviation (SD) (or standard error), median, minimum, and maximum. 95% confidence intervals (CI) will be presented where appropriate for data interpretation.

Categorical data will be summarised in frequency tables with n and percentage. Summaries of a categorical variable will include all recorded values.

The minimum and maximum values will be presented with the same number of decimal places as the raw data collected on the case report form (CRF) (or to 3 significant figures for derived parameters less than 100 and as integers for values more than 99). The mean and percentiles (eg median) will be presented using one additional decimal place. The standard deviation and standard error will be presented using two additional decimal places.

12 Data handling conventions

12.1 Premature withdrawal and missing data

All patients who withdraw prematurely from the study or study drug will be included in the statistical analyses.

If a patient completes the treatment period but has missing data, then this will be made apparent in the patient listings. Missing data will not be imputed.

If the study is prematurely discontinued, all available data will be listed and a review will be carried out to assess which statistical analyses are still considered appropriate.

Data collected at unscheduled time points during the study will not be used in the summaries or data analyses. They will be included in the listings.

If time information (ie hours and/or minutes) for adverse events (AEs) or concomitant medication is missing, but the day is present, then the time will be calculated in days. If date information is partial or missing, then any derived times (eg AE start time from last study medication) will be listed as missing.

12.2 Derived and transformed data

Baseline will be considered to be the latest value obtained before study drug administration (eg before dosing on Day 0, or Screening if not recorded at predose on Day 0 or Day -3).

Laboratory data will be reported in standard units. Out-of-range laboratory tests may be repeated. If a test is out of-range at baseline and repeated before dosing, the latest repeat value before dosing will be used as baseline. However, if a test is out-of-range and repeated at any other time during the study, the out-of-range value (not the repeat value) will be included in statistical summaries.

Triplicate electrocardiogram (ECG) measurements will be taken on screening and the mean of the 3 measurements will be used for analysis. Triplicate vital sign measurements at baseline and the mean of the 3 measurements will be used for analysis.

12.3 Assessment windows

No assessment windows are defined for this report.

12.4 Values of potential clinical importance

A vital signs result will be considered to be of potential clinical importance (PCI) if it falls outside the relevant range below:

Vital Sign	**Range**
Systolic blood pressure	90–140 mm Hg
Diastolic blood pressure	40–90 mm Hg
Pulse rate	40–100 beats/min
Temperature	35.5–37.8°C

QTcF > 450 msec and increases in QTcF from baseline (Day 0, predose) of > 30 msec will be considered to be of PCI.

13 Study population

13.1 Disposition of patients

The disposition of all patients in all populations will be summarised including: number of patients consented, number of patients treated; number completing the study, by treatment; and number withdrawn from the study. The number of screen failures will also be listed and summarised including reason for screen failure.

All patients who withdraw or are withdrawn from the study will be listed, by treatment, with the reason for withdrawal.

A listing of analysis populations will be provided.

13.2 Protocol deviations

Protocol deviations are captured and reviewed (including classification as minor or major) on an ongoing basis during the study, as defined in the Protocol Deviation Plan. Before closing the database, a final review of the protocol deviations will be conducted and an assessment completed to identify any important deviations where data should be excluded from analysis populations.

Potential important protocol deviations are detailed in the Protocol Deviation Plan.

In addition, patients with minor time deviations (measurements taken outside the allowable windows) will be identified. Allowable time windows for pharmacokinetic samples and other procedures are given in Section 6.6 of the study protocol.

Protocol deviations (including time deviations) will be listed by classification and category.

13.3 Demographic and baseline characteristics

Demographic and baseline characteristics will be listed and summarised.

Patients who take concomitant medication will be listed. All non-trial medication will be coded using the latest version of the World Health Organisation (WHO) Drug Global dictionary current at the time of database lock (version March 2024 or higher).

Medical history data will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) which is current at the time of database lock (version 27.0 or higher). All medical history data will be listed.

Alcohol use data (AUD DSM-V score, AUD severity, age of patient when they first recognised a drinking problem) will be listed and summarised. Other drug abuse lifetime use data will also be listed separately and summarised where applicable.

13.4 Treatment compliance

Dates and times of dosing will be listed.

14 Safety analyses

Summaries and listings of safety data will use the safety population.

14.1 Extent of exposure

The dates and times of treatment dosing will be listed to indicate exposure to the study medication.

14.2 Adverse events

AEs will be coded using the version of the MedDRA which is current at the time of database lock (version 27.0 or higher).

All AEs will be listed.

The number of patients with at least one treatment-emergent adverse event (TEAE) per treatment will be tabulated by actual treatment and MedDRA system organ class. A TEAE is defined as an event emerging during treatment (having been absent pre-treatment) or that worsens after treatment[1].

For each of the following, the number of TEAEs and the number of patients with TEAEs will be summarised:

- TEAEs, by system organ class and preferred term
- TEAEs, by system organ class and preferred term and by severity
- Drug-related ("probably" or "possibly" as recorded by the investigator) TEAEs, by system organ class and preferred term.

In addition, a summary of TEAEs by day of onset (Day 0, Days 1-6 and Day 7 or later) will be produced.

Patients with more than one TEAE will be counted only once, at the greatest severity or causality, for each system organ class/preferred term. Multiple TEAEs in a patient will be counted once per system organ class and preferred term. AEs with missing severity and/or causality will be treated as severe and possibly related, respectively.

Summaries will be sorted by system organ class and decreasing total incidence of preferred term.

14.3 Deaths, serious adverse events and other significant adverse events

Deaths and serious adverse events (SAEs) will be listed separately (fatal events separate from non-fatal events). Other significant AEs, as identified by the investigator in the CRF, will be listed separately.

14.4 Adverse events leading to withdrawal from the study

AEs leading to withdrawal will be listed separately.

14.5 Adverse events of special situations (AESS)

AESSs will be listed separately.

14.6 Adverse events of special interest (AESI)

AESIs will be listed separately.

14.7 Clinical laboratory evaluations

Data from haematology, coagulation, clinical chemistry and alcohol biomarkers at each planned assessment, and changes from baseline at each planned post baseline assessment, will be summarised by treatment.

Clinically significant abnormal laboratory tests will be listed. Frequencies of clinically significant postpose abnormal laboratory tests will be summarised.

14.8 Other safety measures

14.8.1 Vital signs

Vital signs at each planned assessment, and change in vital signs from baseline at each planned post baseline assessment, will be summarised by actual treatment.

Plots of individual systolic blood pressure, diastolic blood pressure, and pulse rate against time will be presented for both absolute values and change from baseline by actual treatment.

Vital signs data of PCI will be listed and summarised.

A separate listing of vital sign findings, classified as clinically significant by the investigator will also be provided. Frequency of clinically significant vital signs will be summarised.

The peak (maximum value across all time points for each patient) vital signs (systolic and diastolic blood pressure, and heart rate) at baseline and post dose on day 0 will be listed and summarised.

In addition, the number of patients will be summarised for peak post dose Day 0 under the following categories:

Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart Rate (bpm)
< 130	< 80	<40
130 - 139	80 - 89	40 – 49
140 - 149	90 - 99	50 – 59
150 – 159	100 – 109	60 – 69
160 – 169	110 – 119	70 – 79

170 – 179	120 – 129	80 – 89
180 – 189	130 – 139	90 – 99
190 – 199	>= 140	100 – 109
200 – 209		110 – 119
210 – 219		>120
>= 220		

14.8.2 ECG

QT interval data will be presented using Fridericia's (QTcF) corrections.

ECG variables will be summarised by treatment and time point. Differences from baseline (Day 0, predose) will be summarised by treatment and time point.

Plots of individual QTcF against time will be presented for both absolute values and change from baseline by actual treatment.

The number of patients with a potentially clinically important QTcF value will be summarised by actual treatment and time point, giving the numbers of patients with QTcF > 450 msec, > 480 msec and > 500 msec, and the numbers of patients with increases in QTcF from baseline of > 30 msec and > 60 msec[3]. A supporting listing of all patients with a QTcF value of PCI and a separate listing of ECG findings classified as abnormal by the investigator will also be provided.

The frequency of clinically significant ECG values will be summarised.

14.8.3 Physical examination and cardiac telemetry findings

Abnormal physical examination findings and cardiac telemetry abnormality findings will be listed. Frequencies of clinically significant postpose physical examinations and cardiac telemetry abnormality will be summarised.

14.8.4 Nasal site and throat examination

Abnormal nasal site and throat findings will be listed.

14.8.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

Positive C-SSRS data defined as patients who answered “Yes” to any question will be listed.

14.8.6 Readiness for discharge questionnaire (RDQ)

RDQ data will be listed. Time to discharge calculated from the end time and defined as time when all criteria are met will be calculated for each patient and the mean, median, minimum and maximum calculated by treatment. If end time is missing then it will be imputed with start time.

14.8.7 Reactivation questionnaire (ReAQ)

ReAQ data will be listed. Occurrence (No/Yes), frequency (when the first re-activation took place, number of days after dosing day of first occurrence and number of re-experience or re-activation events in total after dosing), emotional valence (mostly positive, neutral and mostly negative), functional impact (none, mild, moderate and severe for domains; work, social life and family life) and narrative of potential reactivation will be summarised where applicable by treatment and timepoint.

15 Pharmacokinetic analyses

PK concentration data will be summarised using the PK concentration population.

Plasma concentrations of 5-MeO-DMT and its metabolites (bufotenine, 5-methoxyindolacetic acid (5-MIAA) and 5-MeO-DMT-N-Oxide) will be listed and summarised, by treatment, using descriptive statistics. Individual and mean plasma concentration–time profiles will be presented graphically.

For all variables, N (number of patients receiving the treatment in the population), n (number of observations), arithmetic mean, median, minimum, maximum, SD, %CV, and the 95% CI for the arithmetic mean will be provided.

The between-patient CV will be calculated using:

1. %CVb = 100 * (SD/mean) with SD and mean of untransformed data

15.1 Pharmacokinetic concentration data

Plasma concentrations of 5-MeO-DMT and its metabolites (bufotenine, 5-methoxyindolacetic acid (5-MIAA) and 5-MeO-DMT-N-Oxide) will be listed and summarised by treatment.

Using actual sample times, linear and semi-logarithmic concentration-time plots of each patient will be prepared. The same linear and logarithmic scales will be used for each patient. The linear and semi logarithmic plots for a given patient will be presented on the same page. For clarity in presentation, individual profiles for different analytes will be separate.

Nominal blood sampling times will be used to calculate the mean (SD) drug concentrations at each time point. Comparative linear and semi logarithmic plots of the mean (± SD) concentration-time data for each group will be prepared.

For individual concentration–time plots, plasma concentrations below the limit of quantification of the assay (BLQ) will be treated as follows: values that occur before tmax will be taken as zero; all other values will be taken as missing.

For calculation of plasma concentration summary statistics, BLQ values will be taken as zero, unless they fall between two quantifiable concentrations, in which case they will be treated as missing.

16 Pharmacodynamic analyses

PD data will be summarised using the ITT and PP (alcohol use from the TLFB interview, and MEQ only) Population.

PD data will be listed by treatment and time point and summarised by treatment and time point. Changes from baseline questionnaires will be summarised by time point and treatment.

The PD data includes the following psychometric scales and questionnaires: Stanford Expectation of Treatment Scale (SETS), Mystical Experience Questionnaire (MEQ-30), Ego Dissolution Inventory (EDI), 5-Level EuroQol 5-Dimension (EQ-5D-5L), Timeline Follow-Back (TLFB), Montgomery-Åsberg Depression Rating Scale (MADRS), Alcohol Craving Questionnaire (ACQ), Craving Visual Analogue Scale (VAS), Clinical Global Impression of Severity (CGI-S), Patient Global Impression of Change (PGIC), Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar), Short Inventory of Problems (SIP).

Each psychometric scale/questionnaire will be reported using standard scales as described in Appendix A: Pharmacodynamic analysis.

The scales will be listed and summarised.

In addition, an individual plot of the mean units of alcohol per day (UPD) from the TLFB questionnaire will be produced.

17 Changes from the protocol specified statistical analysis

After the study was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee the following changes were made to the analyses:

- Double flagged laboratory values have been updated to report only out of range values

18 References

1. International Conference on Harmonization, 1998. Statistical Principles for Clinical Trials – ICH Harmonised Tripartite Guideline. Guidance for Industry, E9, FDA federal register, Vol 63, 1998, p49583. Available at: http://www.fda.gov/cder/guidance.
2. International Conference on Harmonization, 1995. Structure and Content of Clinical Study Reports – ICH Harmonised Tripartite Guideline. Guidance for Industry, E3, FDA federal register, Vol 61, 1996, p37320. Available at: http://www.fda.gov/cder/guidance.
3. International Conference on Harmonisation, 2005. Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Concept paper, Guidance for Industry, E14, Center for Drug Evaluation and Research (CDER). Available at: http://www.fda.gov/cder/guidance/6922fnl.htm.
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19 ATTACHMENTS

19.1 Table of contents for data display specifications

For overall page layout refer to Appendix B: Sample page .

The numbering in the tables below will take precedence over the numbering in the shells.

The following tables and figures will be produced (templates provided in Section 19.2.1 and 19.2.2):

Table	Description	Population	Source Listing	Template (Shells below)
10.1	Summary of patient disposition	Safety	16.2.1.2, 16.2.1.3, 16.2.3.1	T_SD1
14.1	DEMOGRAPHIC DATA			
14.1.1	Summary of demographic characteristics	Safety	16.2.4.1	T_DM1
14.1.2	Summary of alcohol and drug abuse use data	Safety	16.2.4.4, 16.2.4.5	T_AUDU
14.2	PHARMACOKINETIC AND PHARMACODYNAMIC DATA			
14.2.1.1	Summary of 5MeO-DMT plasma pharmacokinetic concentration-time data [units]	PK Concentration	16.2.6.1	T_PK1
14.2.1.2	Summary of bufotenine plasma pharmacokinetic concentration-time data [units]	PK Concentration	16.2.6.1	T_PK1
14.2.1.3	Summary of 5-methoxyindolacetic acid plasma pharmacokinetic concentration-time data by treatment group [units]	PK Concentration	16.2.6.1	T_PK1
14.2.1.4	Summary of 5-MeO-DMT-N-Oxide plasma pharmacokinetic concentration-time data by treatment group [units]	PK Concentration	16.2.6.1	T_PK1
14.2.2	Summary of Stanford Expectation of Treatment Scale (SETS)	ITT	16.2.6.2	T_PD1
14.2.3.1	Summary of Mystical Experience Questionnaire (MEQ-30) [intent-to-treat population]	ITT	16.2.6.3	T_PD1
14.2.3.2	Summary of Mystical Experience Questionnaire (MEQ-30) [per protocol population]	PP	16.2.6.3	T_PD1
14.2.3.3	Summary of complete mystical experience [intent-to-treat population]	ITT	16.2.6.3	T_PD3
14.2.3.4	Summary of complete mystical experience [per protocol population]	PP	16.2.6.3	T_PD3
14.2.4	Summary of Ego Dissolution Inventory (EDI)	ITT	16.2.6.4	T_PD1
14.2.5	Summary of 5-Level EuroQol 5-Dimension (EQ-5D-5L)	ITT	16.2.6.5	T_PD4
14.2.6.1	Summary of Timeline Follow-Back (TLFB)) [intent-to-treat population]	ITT	16.2.6.6	T_PD1a
14.2.6.2	Summary of Timeline Follow-Back (TLFB) [per protocol population]	PP	16.2.6.6	T_PD1a
14.2.7.1	Summary of Montgomery-Åsberg Depression Rating Scale (MADRS)	ITT	16.2.6.7	T_PD2

Table	Description	Population	Source Listing	Template (Shells below)
14.2.7.2	Summary of patients with 50% reduction from baseline of MADRS scores	ITT	16.2.6.7	T_PD2a
14.2.7.3	Summary of patients in remission based on MADRS scores ≤ 10	ITT	16.2.6.7	T_PD2b
14.2.8	Summary of Alcohol Craving Questionnaire (ACQ)	ITT	16.2.6.8	T_PD2
14.2.9	Summary of Craving Visual Analogue Scale (VAS)	ITT	16.2.6.9	T_PD1
14.2.10	Summary of Clinical Global Impression of Severity (CGI-S)	ITT	16.2.6.10	T_PD6
14.2.11	Summary of Patient Global Impression of Change (PGIC)	ITT	16.2.6.11	T_PD6
14.2.12	Summary of Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar)	ITT	16.2.6.12	T_PD1
14.2.13	Summary of Short Inventory of Problems (SIP)	ITT	16.2.6.13	T_PD2
14.3	SAFETY DATA			
14.3.1.1	Overall summary of treatment-emergent adverse events	Safety	16.2.7.1	T_AE2
14.3.1.2	Summary of treatment-emergent adverse events	Safety	16.2.7.1	T_AE1
14.3.1.3	Summary of drug-related treatment-emergent adverse events	Safety	16.2.7.1	T_AE1
14.3.1.4	Summary of treatment-emergent adverse events by maximum severity	Safety	16.2.7.1	T_AE3
14.3.1.5	Summary of treatment-emergent adverse events by day of onset	Safety	16.2.7.1	T_AE4
14.3.2.1	Listing of fatal adverse events	Safety	16.2.7.1	L_AE1_PG
14.3.2.2	Listing of non-fatal serious adverse events	Safety	16.2.7.1	L_AE1_PG
14.3.2.3	Listing of other significant adverse events	Safety	16.2.7.1	L_AE1_PG
14.3.3	Narratives of deaths, other serious and significant adverse events	Safety		-
14.3.4.1	Summary of post dose clinically significant abnormal laboratory values by treatment and planned relative time	Safety	16.2.8.1, 16.2.8.3, 16.2.8.5	T_LB4
14.3.4.2	Summary of post dose clinically significant abnormal alcohol biomarker values by treatment and planned relative time	Safety	16.2.8.7	T_LB4
14.3.5.1	Summary of chemistry laboratory values	Safety	16.4	T_LB2
14.3.5.2	Summary of haematology laboratory values	Safety	16.4	T_LB2
14.3.5.3	Summary of coagulation laboratory values	Safety	16.4	T_LB2
14.3.5.4	Summary of alcohol biomarker data	Safety	16.4	T_LB2

Table	Description	Population	Source Listing	Template (Shells below)
14.3.6.1	Summary of vital signs	Safety	16.4	T_VS1
14.3.6.2	Summary of vital signs of potential clinical importance by treatment, planned relative time and parameter	Safety	16.2.9.1	T_VS2
14.3.6.3	Summary of vital signs of potential clinical importance by parameter and treatment (excluding baseline time point)	Safety	16.2.9.1	T_VS3
14.3.6.4	Summary of post dose clinically significant vital signs	Safety	16.2.9.2	T_VS4
14.3.6.5	Summary of peak vital signs ranges by treatment, ranges and parameter – Day 0 post dose	Safety	16.2.9.3	T_VS5
14.3.6.6	Summary of peak vital signs by treatment and parameter - baseline and day 0 post dose	Safety	16.2.9.3	T_VS6
14.3.7.1	Summary of ECG values	Safety	16.4	T_EG2
14.3.7.2	Summary of QTcF values and changes in QTcF values of potential clinical importance by treatment, planned relative time and category	Safety	16.2.9.4	T_EG3
14.3.7.3	Summary of post dose clinically significant ECG values	Safety	16.2.9.5	T_EG5
14.3.7.4	Summary of post dose clinically significant cardiac telemetry abnormalities	Safety	16.2.9.6	T_EG5
14.3.7.5	Summary of post dose clinically significant physical examination findings	Safety	16.2.9.7	T_EG5
14.3.7.6	Summary of post dose clinically significant nasal site and throat reaction findings	Safety	16.2.9.8	T_EG5
14.3.7.7	Summary of readiness of discharge questionnaire (RDQ)-Time to discharge (units)	Safety	16.2.9.10	T_RDQ
14.3.7.8	Summary of re-activation questionnaire (ReAQ)	Safety	16.2.9.11	T_ReAQ

Figure	Description	Population	Source Listing	Template (Shells below)
14.2	PHARMACOKINETIC AND PHARMACODYNAMIC DATA			
14.2.1.1	Individual 5MeO-DMT plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1	F_PK1
14.2.1.2	Mean (+/- SD) 5MeO-DMT plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1	F_PK2
14.2.1.3	Mean 5-MeO-DMT plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1	F_PK2
14.2.2.1	Individual bufotenine plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1	F_PK1
14.2.2.2	Mean (+/- SD) bufotenine plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1	F_PK2
14.2.2.3	Mean bufotenine plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1	F_PK2
14.2.3.1	Individual 5-methoxyindolacetic acid plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1	F_PK1
14.2.3.2	Mean (+/- SD) 5-methoxyindolacetic acid plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1	F_PK2
14.2.3.3	Mean 5-methoxyindolacetic acid plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1	F_PK2
14.2.4.1	Individual 5-MeO-DMT-N-Oxide plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1	F_PK1
14.2.4.2	Mean (+/- SD) 5-MeO-DMT-N-Oxide plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1	F_PK2
14.2.4.3	Mean 5-MeO-DMT-N-Oxide plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1	F_PK2
14.2.5.1	Individual mean units of alcohol per day (UPD)-time plots [intent-to-treat population]	ITT	16.2.6.6	F_PD
14.2.5.2	Individual mean units of alcohol per day (UPD)-time plots [per protocol population]	PP	16.2.6.6	F_PD
14.3	SAFETY DATA			

14.3.1	Individual systolic blood pressure-time plots	Safety	16.4	F_SAF1
14.3.2	Individual diastolic blood pressure-time plots	Safety	16.4	F_SAF1
14.3.3	Individual heart rate-time plots	Safety	16.4	F_SAF1
14.3.4	Individual QTcF-time plots	Safety	16.4	F_SAF1

The following abbreviated listings will be produced (templates provided in Section 19.2.3):

Listing	Description	Template (Shells below)
16.2.1	Study dates & disposition of patients	
16.2.1.1	Listing of study dates	L_SD1_PG
16.2.1.2	Listing of reasons for withdrawal	L_SD2_PG
16.2.1.3	Listing of patients screened but not enrolled	L_SD3_PG
16.2.2	Protocol deviations	
16.2.2.1	Listing of patients with time deviations	L_TD1_PG
16.2.2.2	Listing of patients with minor protocol deviations	L_DV2_PG
16.2.2.3	Listing of patients with major protocol deviations	L_DV2_PG
16.2.3	Analysis sets, including patients excluded from analysis	
16.2.3.1	Listing of analysis populations	L_AN1_PG
16.2.4	Demographic data & concomitant medication	
16.2.4.1	Listing of demographic characteristics	L_DM1_PG
16.2.4.2	Listing of concomitant medications	L_CM1_PG
16.2.4.3	Listing of medical history	L_MH1_PG
16.2.4.4	Listing of alcohol use history	L_AUH_PG
16.2.4.5	Listing of drug abuse use history	L_DUH_PG
16.2.5	Study drug administration	
16.2.5.1	Listing of exposure data	L_EX1_PG
16.2.6	Pharmacokinetic and Pharmacodynamic data	
16.2.6.1	Listing of 5MeO-DMT,bufotenine, 5-methoxyindolacetic acid and 5-MeO-DMT-N-Oxide plasma pharmacokinetic concentration-time data	L_PK1_PG
16.2.6.2	Listing of Stanford Expectation of Treatment Scale (SETS)	L_PD4_PG

Listing	Description	Template (Shells below)
16.2.6.3	Listing of Mystical Experience Questionnaire (MEQ-30)	L_PD2_PG
16.2.6.4	Listing of Ego Dissolution Inventory (EDI)	L_PD3_PG
16.2.6.5	Listing of 5-Level EuroQol 5-Dimension (EQ-5D-5L)	L_PD5_PG
16.2.6.6	Listing of Timeline Follow-Back (TLFB)	L_PD6_PG
16.2.6.7	Listing of Montgomery-Åsberg Depression Rating Scale (MADRS)	L_PD4a_PG
16.2.6.8	Listing of Alcohol Craving Questionnaire (ACQ)	L_PD7_PG
16.2.6.9	Listing of Craving Visual Analogue Scale (VAS)	L_PD3_PG
16.2.6.10	Listing of Clinical Global Impression of Severity (CGI-S)	L_PD8_PG
16.2.6.11	Listing of Patient Global Impression of Change (PGIC)	L_PD8_PG
16.2.6.12	Listing of Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar)	L_PD9_PG
16.2.6.13	Listing of Short Inventory of Problems (SIP)	L_PD2_PG
16.2.7	Adverse events	
16.2.7.1	Listing of all adverse events	L_AE1_PG
16.2.7.2	Listing of serious adverse events	L_AE1_PG
16.2.7.3	Listing of adverse events leading to withdrawal from study	L_AE1_PG
16.2.7.4	Listing of adverse events of special situation (AESS)	L_AE1_PG
16.2.7.5	Listing of adverse events of special interest (AESI)	L_AE1_PG
16.2.8	Laboratory values	
16.2.8.1	Listing of post dose clinically significant abnormal chemistry laboratory values	L_LB1_PG
16.2.8.2	Listing of all clinical chemistry laboratory data for patients with post dose clinically significant abnormal chemistry laboratory values	L_LB1_PG
16.2.8.3	Listing of post dose clinically significant abnormal haematology laboratory values	L_LB1_PG
16.2.8.4	Listing of all haematology laboratory data for patients with post dose clinically significant abnormal haematology laboratory values	L_LB1_PG
16.2.8.5	Listing of post dose clinically significant abnormal coagulation laboratory values	L_LB1_PG
16.2.8.6	Listing of all coagulation laboratory data for patients with post dose clinically significant abnormal coagulation laboratory values	L_LB1_PG
16.2.8.7	Listing of post dose clinically significant abnormal alcohol biomarker values	L_LB1_PG
16.2.8.8	Listing of all alcohol biomarker data for patients with post dose clinically significant abnormal alcohol biomarker values	L_LB1_PG

Listing	Description	Template (Shells below)
16.2.9	Vital signs, ECG variables physical findings nasal site reactions, C-SSRS, RDQ and ReAQ data	
16.2.9.1	Listing of vital signs of potential clinical importance	L_VS1_PG
16.2.9.2	Listing of clinically significant vital signs	L_VS2_PG
16.2.9.3	Listing of peak vital signs data	L_VS3_PG
16.2.9.4	Listing of QTcF values of potential clinical importance	L_EG1_PG
16.2.9.5	Listing of abnormal ECG findings	L_EG2_PG
16.2.9.6	Listing of abnormal cardiac telemetry findings	L_EG3_PG
16.2.9.7	Listing of abnormal physical examination findings	L_PE1_PG
16.2.9.8	Listing of abnormal nasal site and throat examination findings	L_NSE1_PG
16.2.9.9	Listing of positive Columbia-Suicide Severity Rating Scale (C-SSRS) data	L_CSS_PG
16.2.9.10	Listing of Readiness of Discharge Questionnaire (RDQ)	L_RDQ_PG
16.2.9.11	Listing of re-activation questionnaire (ReAQ)	L_ReAQ_PG

Complete listings of all data collected in this study will also be produced separately.

19.2 Data display specifications

19.2.1 Table Outlines

Template T_SD1

Table 10.1 Summary of patient disposition

Population	Status	Reason for Discontinuation/Withdrawal	All Patients (N=xx) n (%)
Screened	Total		
	Included		
	Excluded	Not satisfying inclusion/exclusion criteria	
		Declined to participate	
		Other	
Safety	Included		xx
	Completed		xx (xx)
	Withdrawn		xx (xx)
		Death	xx (xx)
		Adverse Events	xx (xx)
		Withdrawal by patient	xx (xx)
		Study terminated by Sponsor	xx (xx)
		Lost to follow-up	xx (xx)
		Other	xx (xx)
PK concentration	Included		xx (xx)
Intent-to-treat	Included		xx (xx)
Per protocol			

Source: Listing 16.2.xx

Template T_DM1

Table 14.1 Summary of demographic characteristics

Variable	Statistics	Treatment 1 (N=xx)
Age (y)	n	
	Mean	
	SD	
	Median	
	Min	
	Max	
Sex (%)	Female	
	Male	
Race (%)	American Indian or	
	Alaskan Native	
	Asian	
	Black	
	Native Hawaiian or other	
	Pacific Islander	
	White	
	Other	
Ethnicity (%)	Hispanic or Latino	
	Not Hispanic or Latino	
Height (cm)	n	
	Mean	
	SD	
	Median	
	Min	
	Max	
Weight (kg)	n	
	Mean	
	SD	
	Median	
	Min	
	Max	

Source: Listing 16.2.xx

Programming notes: Continued with all additional demographic characteristics

Template T_AUDU

Table 14.2.2.xx Summary of alcohol and drug abuse use history data

Variable	Statistics	Treatment 1 (N=xx)
Age Drinking Problem Recognised (years)	n	
	Mean	
	SD	
	Median	
	Min	
	Max	
AUD DSM-V Score	n	
	Mean	
	SD	
	Median	
	Min	
	Max	
AUD Severity (number of DSM-V Symptoms) (%)	Mild (2-3 criteria)	
	Moderate (4-5 criteria)	
	Severe (6 or more criteria)	
Drug 1 (%)	Yes	
	No	
Drug 2 (%)	Yes	
	No	

Source: Listing 16.2.xx

AUD= Alcohol use disorder

Programming notes: Continued with all Items assessed, and drug used as recorded

Template T_PK1

Table 14..2.xx Summary of 5-MeO-DMT plasma pharmacokinetic concentration-time data [units]

Treatment	{Add. time var.}	Planned Relative Time	n	No. Imputed	Mean	95% CI (Lower,Upper)	SD	%CVb	Median	Min	Max
Treatment 1		5 min	x	x	xxxx.x	(xxxx.x,xxxx.x)		xx.x	xxxx.x	xxxx	xxxx
(N=xx)		15 min	x	x	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xx.x	xxxx.x	xxxx	xxxx
		60 min	x	x	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xx.x	xxxx.x	xxxx	xxxx

Source: Listing 16.2.xx

Programming notes: Continued with all timepoints

Template T_PD1

Table 14.2.2.xx Summary of Stanford Expectations of Treatment Scale (SETS)

Score	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max
Positive Expectancy	Treatment 1 (N=xx)							
Negative Expectancy	Treatment 1 (N=xx)							

Source: Listing 16.2.xx

Programming notes: For EDI and visual analogue scale, the first column will be "Score (mm)". Include all subscales are stated in appendix A

Template T_PD1a

Table 14.2.2.xx Summary of Timeline Follow-Back (TLFB) [intent-to-treat population]

									Change from Baseline					
Scoring Item	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Longest continuous number of abstinence (days)	Treatment 1 (N=xx)		x	x.x	x.xx	x.x	x	x						
Max number of standard units of alcohol consumed on any one day	Treatment 1 (N=xx)	85 Days Prior Day-3	x	x.x	x.xx	x.x	x	x						
		Day 14	x	x.x	x.xx	x.x	x	x						
		Day 28	x	x.x	x.xx	x.x	x	x						
		Day 56	x	x.x	x.xx	x.x	x	x						
		Day 84	x	x.x	x.xx	x.x	x	x						
Number of Heavy Drinking Days (HDD)	Treatment 1 (N=xx)	85 Days Prior Day-3	x	x.x	x.xx	x.x	x	x						
		Day 14	x	x.x	x.xx	x.x	x	x						
		Day 28	x	x.x	x.xx	x.x	x	x						
		Day 56	x	x.x	x.xx	x.x	x	x						
		Day 84	x	x.x	x.xx	x.x	x	x						
Number of days after dosing to first drink	Treatment 1 (N=xx)		x	x.x	x.xx	x.x	x	x						
Number of days after dosing to first HDD	Treatment 1 (N=xx)		x	x.x	x.xx	x.x	x	x						
Average number of standard units of alcohol consumed per week	Treatment 1 (N=xx)	85 Days Prior Day-3	x	x.x	x.xx	x.x	x	x						
		Day 14	x	x.x	x.xx	x.x	x	x	x	x.x	x.xx	x.x	x	x
		Day 28	x	x.x	x.xx	x.x	x	x	x	x.x	x.xx	x.x	x	x
		Day 56	x	x.x	x.xx	x.x	x	x	x	x.x	x.xx	x.x	x	x
		Day 84	x	x.x	x.xx	x.x	x	x	x	x.x	x.xx	x.x	x	x
Percentage of Heavy Drinking Days (PHDD)	Treatment 1 (N=xx)	85 Days Prior Day-3	x	x.x	x.xx	x.x	x	x						
		Day 14	x	x.x	x.xx	x.x	x	x	x	x.x	x.xx	x.x	x	x
		Day 28	x	x.x	x.xx	x.x	x	x	x	x.x	x.xx	x.x	x	x
		Day 56	x	x.x	x.xx	x.x	x	x	x	x.x	x.xx	x.x	x	x
		Day 84	x	x.x	x.xx	x.x	x	x	x	x.x	x.xx	x.x	x	x
Percentage of Drinking Days (PDD)	Treatment 1 (N=xx)		x	x.x	x.xx	x.x	x	x	x	x.x	x.xx	x.x	x	x
Mean Units per Day (UPD)	Treatment 1 (N=xx)		x	x.x	x.xx	x.x	x	x	x	x.x	x.xx	x.x	x	x

Abstinence: Percentage of Abstinent Days (PAD)	Treatment 1 (N=xx)	x	x.x	x.xx	x.x	x	x	x	x.x	x.xx	x.x	x	x			

Source: Listing 16.2.xx

Note: 85 Days Prior Day -3 = 85 Days Prior Day -3 (or start of detox)

Programming notes: *Continued with all the timepoints (*85 Days Prior Day-3, Day 14, Day 28, Day 56 and Day 84*) for PDD, UPD and PAD*

Template T_PD2

Table 14.2.2.xx Summary of Montgomery-Åsberg Depression Rating Scale (MADRS) [intent-to-treat population]

									Change from Baseline					
Question	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Apparent Sadness	Treatment 1 (N=xx)													
↓														
Total MADRS Score	Treatment 1 (N=xx)													

Source: Listing 16.2.xx

Programming notes: *For MADRS, include all individual questions treated as continuous data*
Continued for all scores (subscales and/or total score) & time points for all questionnaires described in Appendix A. Update column 1 to match the data
*For Alcohol Craving questionnaire, the first column will be "*Scoring Item*"*

Template T_PD2a

Table 14.3.4.xx Summary of patients with 50% reduction from baseline of MADRS scores

	Responder at Day 28	Responder at Day 56	Responder at Day 84
Treatment	n (%)	n (%)	n (%)
Treatment 1 (N=xx)			

Source: Listing 16.2.xx

Note: Percentages are based on the number of non-missing observations

Programming notes: *Continued with all time points*

Template T_PD2b

Table 14.3.4.xx Summary of patients in remission based on MADRS scores ≤ 10

Treatment	Planned Relative Time	Total MADRS score <= 10 n (%)
Treatment 1 (N=xx)	Time 1	

Source: Listing 16.2.xx

Note: Percentages are based on the number of non-missing observations

Programming notes: Continued with time points.

Template T_PD3

Table 14.2.2.xx Summary of complete mystical experience

Planned Relative Time	Treatment 1 (N=xx) n (%)
Time 1	

Source: Listing 16.2.xx

A complete mystical experience is defined as a patient scoring 3 or more on each of the four subdomains

Programming notes: Continued for all timepoints

Template T_PD4

Table 14.2.2.xx Summary of 5-Level EuroQol 5-Dimension (EQ-5D-5L)

Item Assessed	Question	Planned Relative Time	Treatment 1 (N=xx)
Mobility (%)	I have no problems in walking about	Time 1	
		Time 2	
	I have slight problems in walking about	Time 1	
		Time 2	
	I have moderate problems in walking about	Time 1	
	↓		
Self-care (%)	I have no problems washing or dressing myself	Time 1	
	↓	Time 2	
Usual activities (%)	I have no problems doing my usual activities	Time 1	
	↓		
Pain/Discomfort (%)	I have no pain or discomfort	Time 1	
	↓		
Anxiety/Depression (%)	I am not anxious or depressed	Time 1	
	↓		
How good or bad your	n	Time 1	
health is today (mm)	Mean		
	SD		
	Median		
	Min		
	Max		

Programming notes: Continued with all Items assessed, questions, treatment groups and time points.

Template T_PD5

Table 14.2.2.xx Summary of Montgomery-Asberg Depression Rating Scale (MADRS)

									Change from Baseline					
Question	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Apparent Sadness	Treatment 1 (N=xx)													
↓														
Total MADRS Score	Treatment 1 (N=xx)													

Source: Listing 16.2.xx

Programming notes: *Continued with all questions, and time points.*

Template T_PD6

Table 14.2.3.xx Summary of Clinical Global Impression-Severity (CGI-S)

								Change from Baseline					
Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Treatment 1 (N=xx)													

Source: Listing 16.2.xx

Programming notes: *Continued for all time points. Treat the data as continuous*
Change from baseline is not required for PGIC

Template T_AE1

Table 14.3.3.xx Summary of treatment-emergent adverse events

System Organ Class*	Preferred Term	Treatment 1 (N=xx) n (%)
Number of patients with TEAEs		x (xx.x)
Gastrointestinal disorders	Total number of patients	x (xx.x)
	Abdominal discomfort	x (xx.x) [xx]
	Abdominal pain	x (xx.x) [xx]
	↓	
Nervous system disorders	Total number of patients	x (xx.x)
	Dizziness	x (xx.x) [xx]
	Headache	x (xx.x) [xx]
	↓	
↓	↓	

Source: Listing 16.2.xx

n = number of patients (patients with >1 TEAE are counted only once per system organ class and preferred term)

[ ] = number of TEAEs

*Coded using MedDRA version xx.x

rogramming notes: *SOCs and PTs are sorted in decreasing order of frequency*

Presented for all applicable MedDRA system organ classes and terms.

Template T_AE2

Table 14.3.3.xx Overall summary of treatment-emergent adverse events

Number of Patients with	Treatment 1 (N=xx) n (%)	
Any TEAE	x (xx.x)	[xx]
Any serious TEAE	x (xx.x)	[xx]
Any drug-related TEAE	x (xx.x)	[xx]
Any TEAE leading to withdrawal	x (xx.x)	[xx]
Any TEAE with mild as worst severity	x (xx.x)	
Any TEAE with moderate as worst severity	x (xx.x)	
Any TEAE with severe as worst severity	x (xx.x)	
Any TEAE with life-threatening as worst severity	x (xx.x)	

Source: Listing 16.2.xx

n = number of patients
[ ] = number of TEAEs

Template T_AE3

Table 14.3.3.xx Summary of treatment-emergent adverse events by maximum severity

System Organ Class*	Preferred Term	Severity	Treatment 1 (N=xx) n (%)
Number of TEAEs		Mild	x (xx.x)
		Moderate	x (xx.x)
		↓	
Gastrointestinal disorders	Total number of patients	Mild	x (xx.x)
		Moderate	x (xx.x)
	Abdominal discomfort	Mild	x (xx.x)
	Abdominal pain	Mild	x (xx.x)
	↓		

Source: Listing 16.2.xx

n = number of patients (patients with >1 TEAE are counted only once per system organ class and preferred term)
*Coded using MedDRA version xx.x

Programming notes: *Each preferred term counted only once across all severities for each patient*
SOCs and PTs are sorted in decreasing order of frequency
Presented for all applicable MedDRA system organ classes and terms.

Template T_AE4

Table 14.3.3.xx Summary of treatment-emergent adverse events by day of onset

System Organ Class*	Preferred Term	Day of Onset	Treatment 1 (N=xx n (%)
Nervous system disorders	Dizziness	Day 0	x (xx)
		Days 1-6	x (xx)
		>=Day 7	x (xx)
	Headache	Day 0	x (xx)
	↓	Days 1-6	x (xx)
		>=Day 7	x (xx)
Gastrointestinal disorders	Abdominal discomfort	Day 0	x (xx)
		Days 1-6	x (xx)
		>=Day 7	x (xx)

Source: Listing 16.2.xx

n = number of patients
*Coded using MedDRA version xx.x

Programming notes: *SOCs and PTs are sorted in decreasing order of frequency*
Presented for all applicable MedDRA system organ classes and terms.

Template T_LB4

Table 14.3.4.xx Summary of post dose clinically significant abnormal laboratory values by treatment and planned relative time

Laboratory Test (units)	Treatment	Planned Relative Time	Clinically Significant n (%)
	Treatment 1 (N=xx)		

Source: Listing 16.2.xx

Programming notes: Continued with all tests, and time points.

Template T_LB2

Table 14.3.5.xx Summary of chemistry laboratory values

									Change from Baseline					
Laboratory Test (units)	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
	Treatment 1 (N=xx)													

Source: Listing 16.2.xx

Programming notes: Continued with all time points

Template T_VS1

Table 14.3.6.xx Summary of vital signs

									Change from Baseline					
Variable (units)	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Systolic Blood Pressure (mmHg)	Treatment 1 (N=xx)													

Source: Listing 16.2.xx

Programming notes: *Continued with all variables, and time points*

Template T_VS2

Table 14.3.6.xx Summary of vital signs of potential clinical importance

		Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)		Heart Rate (beats/min)		Temperature (C)		etc	
Treatment	Planned Relative Time	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Treatment 1 (N=xx)	Time 1										
	Time 2										

Source: Listing 16.2.xx

Programming notes: *Continued with all parameters. n = total number of results for that parameter*

Template T_VS3

Table 14.3.6.xx Summary of vital signs of potential clinical importance by parameter and treatment (excluding baseline time point)

	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)		Heart Rate (beats/min)		Temperature (C)		etc		Overall*	
Treatment	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Treatment 1 (N=xx)												

Source: Listing 16.2.xx

Patients only counted once per parameter

*Patients only counted once per treatment

Programming notes: *Continued with all parameters. n = total number of results for that parameter*
Only include post-treatment time points

Template T_VS4

Table 14.3.6.xx Summary of post dose clinically significant vital signs

		Clinically Significant	
Treatment	Planned Relative Time	n	(%)
Treatment 1 (N=xx)	Time 1		
	Time 2		

Programming notes: *Continued with all timepoints. n = total number of results for that parameter*

Template T_VS5

Table 14.3.7.xx Summary of peak Vital Signs ranges by treatment, ranges and parameter - Day 0 post dose

	Systolic Blood Pressure (mm Hg)										
Treatment	<130 n (%)	130 - 139 n (%)	140 – 149 n (%)	150 – 159 n (%)	160 – 169 n (%)	170 – 179 n (%)	180 – 189 n (%)	190 – 199 n (%)	200 - 209 n (%)	210 – 219 n (%)	> =220 n (%)
Treatment 1 (N=xx)											

Source: Listing 16.2.xx

The maximum value across all time points per subject is used for analysis.

Programming notes: *Continued with all variables . n = total number of results for that parameter.*
Continued with all the ranges in ***section 14.8.1***

Template T_VS6

Table 14.3.6.xx Summary of peak vital signs by treatment and parameter - baseline and Day 0 post dose

Variable (units)	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max
Systolic Blood Pressure (mmHg)	Treatment 1 (N=xx)	Predose Day 0, Postdose						

Source: Listing 16.2.xx

Programming notes: *Continued with DBP and HR. The maximum value across all time points per subject are used for analysis.*

Template T_EG2

Table 14.3.7.xx Summary of ECG values

									Change from Baseline					
Variable (units)	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Heart Rate (bpm)	Treatment 1 (N=xx)													
PR Interval (msec)	Treatment 1 (N=xx)													

Source: Listing 16.2.xx

Programming notes: *Continued with all time points*
Do not summarise RR or QRS axis

Template T_EG3

Table 14.3.7.xx Summary of QTcF values and changes in QTcF values of potential clinical importance

								>30-60 msec Increase		>60 msec Increase	
Treatment	Planned Relative Time	451 – 480 msec n	(%)	481 – 500 msec n	(%)	> 500 msec n	(%)	n	(%)	n	(%)
Treatment 1 (N=xx)	Time 1										
	Time 2										
	Time 3										

Source: Listing 16.2.xx

Programming notes: *Continued with all time points. n = total number of results for that parameter*

Template T_EG5

Table 14.3.7.xx Summary of clinically significant ECG values

Treatment	Planned Relative Time	Abnormal CS n	(%)
Treatment 1	Time 1		
(N=xx)	Time 2		

Source: Listing 16.2.xx

Programming notes: *Continued with all timepoints. n = total number of results for that parameter*
For cardiac telemetry, change planned relative time to Start and End date/time

Template T_RDQ

Table 14.3.7.xx Summary of readiness of discharge questionnaire (RDQ)- Time to discharge (units)

Treatment	Planned Relative Time	n	Mean	Median	Min	Max
Treatment 1 (N=xx)						

Source: Listing 16.2.xx

Programming notes: *Continued with all time points*

Template T_ReAQ_PG _

Table 14.3.8.xx Summary of re-activation questionnaire (ReAQ)

Assessment	Planned Relative Time		Treatment 1 (N=xx)
Number of Patients with Re-activation (%)	Time 1	Yes	
		No	
	Time 2		
Number of Days after dose (Days)	Time 1	n	
		Mean	
		SD	
		Median	
		Min	
		Max	
Number of Re-activation events	Time 1	n	
		Mean	
		SD	
		Median	
		Min	
		Max	
Emotional Valence	Time 1	Mostly Positive	
		Neutral	
		Mostly	
		Negative	
Functional Impact- Work (%)	Time 1	None	
		Mild	
		Moderate	
		Severe	
	Time 2		
Functional Impact- Social Life (%)	Time 1	None	
		Mild	
		Moderate	
		Severe	
	Time 2		

Functional Impact- Family Life (%)	Time 1	None
		Mild
		Moderate
		Severe

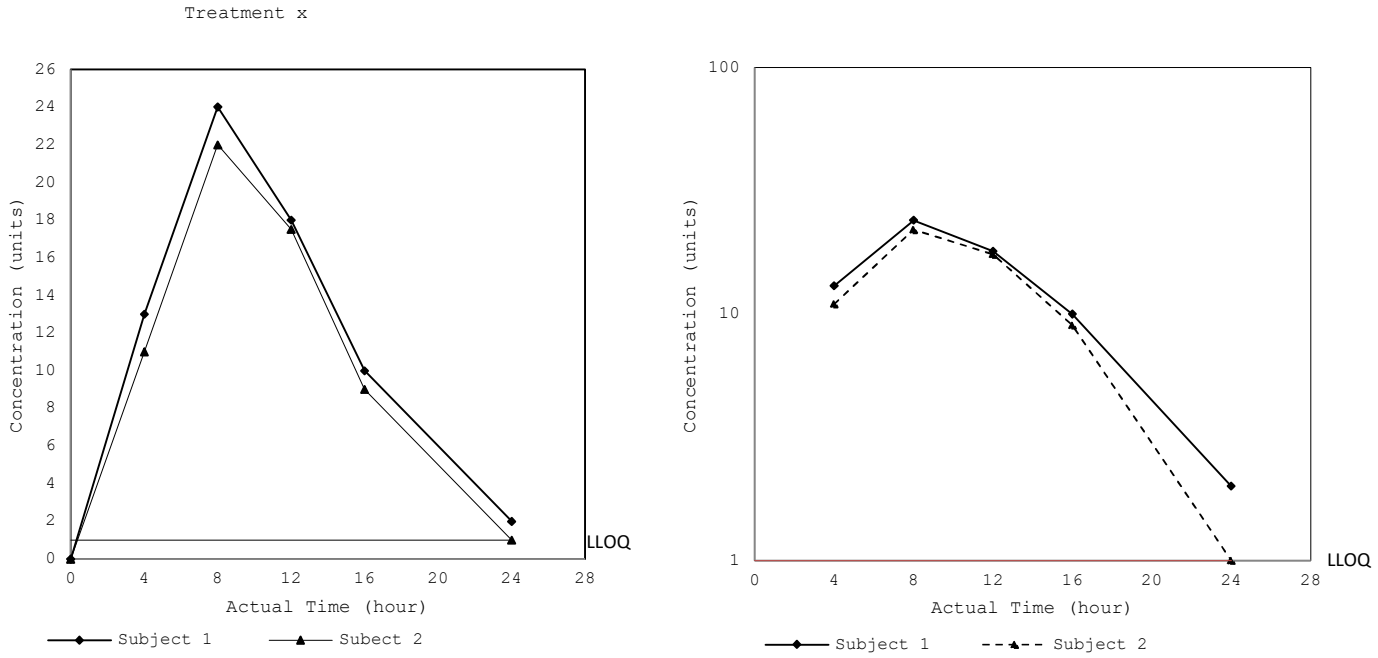
Source: Listing 16.2.xx

Programming notes: *Continued with all assessments and timepoints. Occurrence* =Number of patients with Re-activation).
Denominator for percentages will be total number of scores recorded (excluding N/A) at relative time point

19.2.2 Figure Outlines

Template F_PK1

Figure 14.2.xx Individual 5-MeO-DMT plasma concentration-time plots (linear and semi-log)

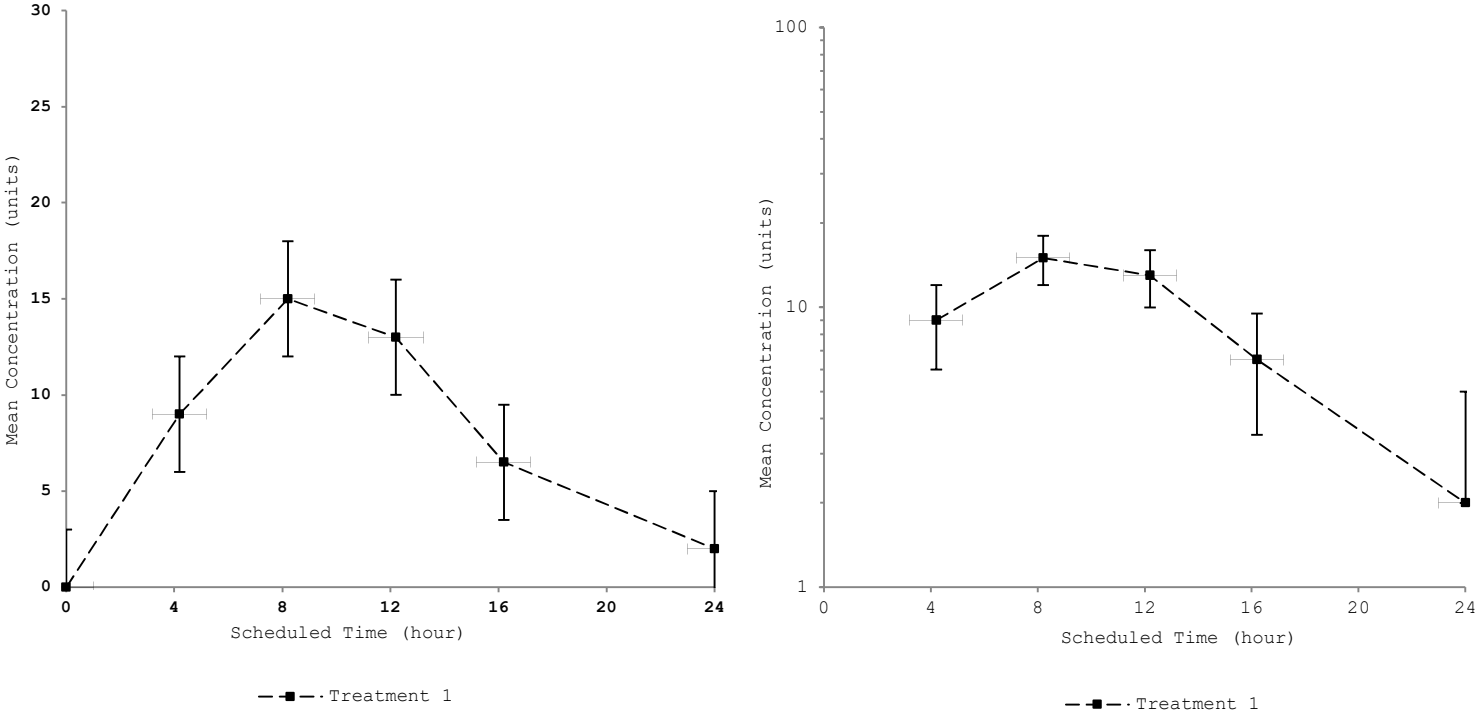


Source: Listing 16.2.xx

Programming notes: *Page by treatment and include all Patients on same page*

Template F_PK2

Figure 14.2.xx Mean (+/- SD) 5-MeO-DMT plasma concentration-time plots (linear and semi-log)

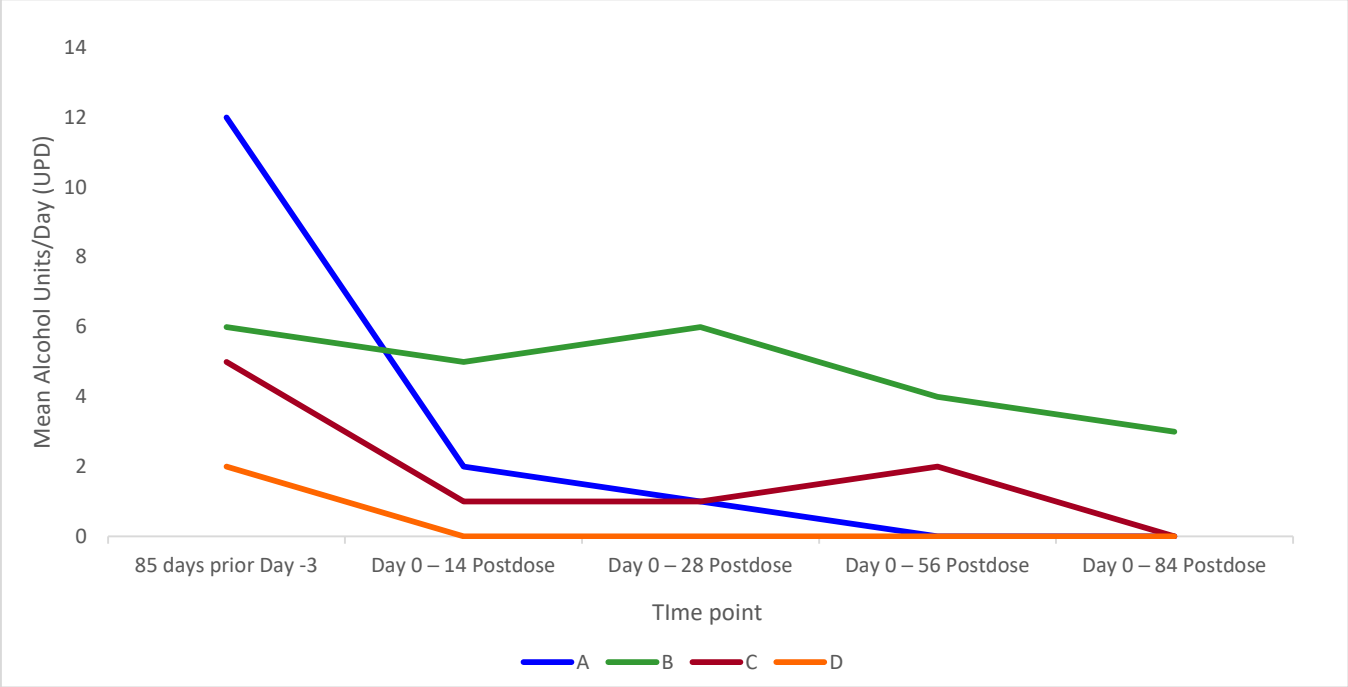


Source: Listing 16.2.xx

BLQ values are imputed to zero

Template F_PD

Figure 14.2.xx Individual mean units of alcohol per day (UPD)-time plots [intent-to-treat population]

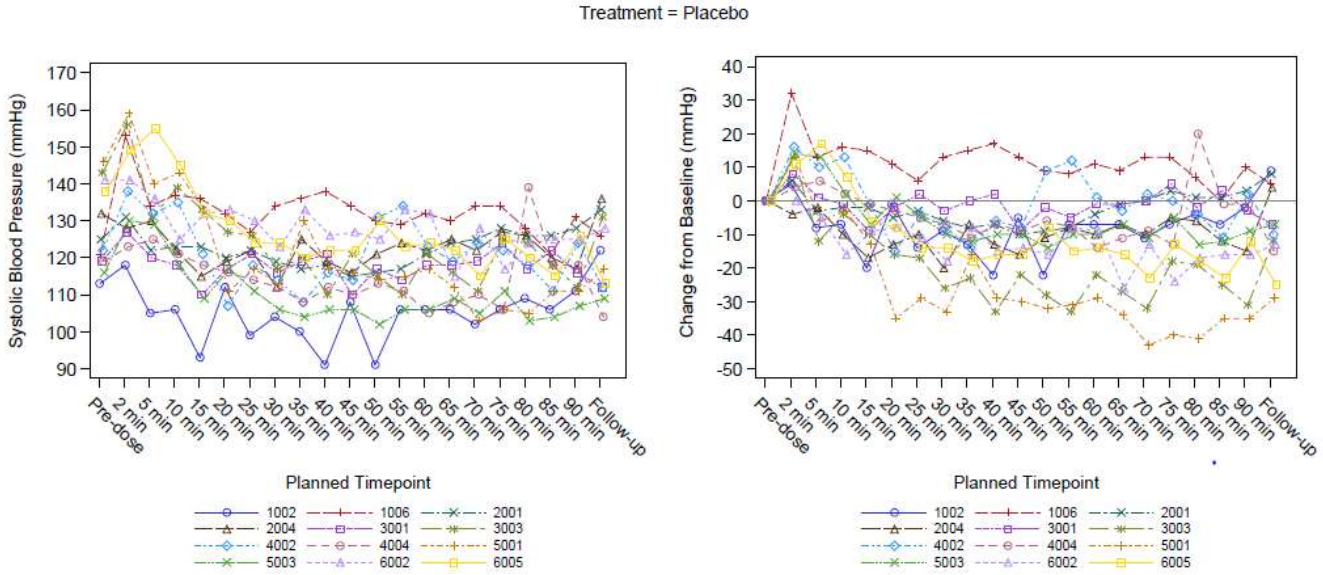


Source: Listing 16.2.xx

Programming notes: *Include all Patients with a patient legend*

Template F_SAF1

Figure 14.3.1 Individual systolic blood pressure-time plots



Source: Listing 16.xx

Programming note: Continue with all parameters
Update the x-axis label to "Planned Relative Time"

19.2.3 Listing Outlines

Template L_SD1_PG

Listing 16.2.x.xx Listing of study dates

				Follow Up		
Treatment	Patient	Screening	Day 0	Day 1	Day x	Day 84

Programming notes: *Lists dates for screening, dosing Day and follow up days*
If a repeat screening was done, report the original and if a repeat FU was done, report the repeat FU

Template L_SD2_PG

Listing 16.2.x.xx Listing of reasons for withdrawal

Treatment	Patient	Date of Withdrawal	Study Day	Reason

Programming notes: *Reason for withdrawal is concatenation of reason and details*

Template L_SD3_PG

Listing 16.2.x.xx Listing of patients screened but not enrolled

Screen Number	Date of Screen	Failure Category	Details

Template L_TD1_PG

Listing 16.2.x.xx Listing of patients with time deviations

Treatment	Patient	Planned Relative Time	Procedure	Allowed deviation (h:min)	Actual deviation (h:min)	Time outside the deviation window (h:min)

Programming notes: Only include time deviations which exceed the allowed deviation

Template L_DV2_PG

Listing 16.2.x.xx Listing of patients with minor protocol deviations

Treatment	Patient	Protocol Deviation	Type of Deviation

Programming notes: Protocol deviation is in the form "Time x: DVTERM". Separate listing for minor and major protocol deviations

Template L_AN1_PG

Listing 16.2.x.xx Listing of analysis populations

Treatment	Patient	Safety Population	Population 1	Population 2

Template L_DM1_PG

Listing 16.2.x.xx Listing of demographic characteristics

Treatment	Patient	Date of visit	Year of birth	Age (y)	Sex	Race	Ethnicity	Height (cm)	Weight (kg)
↓	↓								

Programming notes: *Continued with all patients and other demographic characteristics. Include baseline weight and height*

Template L_CM1_PG

Listing 16.2.x.xx Listing of concomitant medications

Treatment	Patient	Medication Class/ Medication Code*	Drug Name/ Indication	Dose/ Freq/Route	Date/time Started/ Date Stopped	Study Day Started/ Time Since Last Dose	Started Pre-Dose?	Ongoing Medication?

*Coded using WHODrug Global vXX.X

Programming notes: *Include dose and units (e.g. 5 mg)/Freq/Route*

Template L_MH1_PG

Listing 16.2.x.xx Listing of medical history

Treatment	Patient	Category	System organ class*/Preferred term	Verbatim text	Clinical significance	Date Started	Date Stopped	End relative to Screening

*Coded using MedDRA vXX.X

Template L_AUH_PG

Listing 16.2.x.xx Listing of alcohol use history data

Treatment	Patient	Date of Admission for Treatment of Current AUD Episode	Age Drinking Problem Recognised	AUD DSM-V Score	AUD Severity (number of DSM-V Symptoms)	Abstinence Details

AUD= Alcohol use disorder

Template L_DUH_PG

Listing 16.2.x.xx Listing of drug abuse use history data

Treatment	Patient	Drug Type Used in Lifetime	Result
		Drug 1	Yes
		Drug 2	Yes
		etc	Yes

Programming notes: Continued with all drug types. Only list where Result is "Yes"

Template L_EX1_PG

Listing 16.2.x.xx Listing of exposure data

Treatment	Patient	Start Date/ Start Time of Dose	Dose	Dose Unit	Formulation/ Route	Frequency
Treatment 1	1001	01JAN2002/23:59	25	mg	Tablet/ Oral	Once

Template L_PK1_PG

Listing 16.2.6.xx Listing of 5-MeO-DMT and bufotenine plasma pharmacokinetic concentration-time data

Treatment	Patient	Date	Planned Relative Time	Actual time (hh:mm)	Time Deviation (min)	Actual Relative Time (h)	Concentration (units)			
							5-MeO-DMT	Bufotenine	5-methoxyindolacetic acid	5-MeO-DMT-N-Oxide

Below the Limit of Quantification (BLQ) is < xx *units for* 5-MeO-DMT, *< xx units for bufotenine, < xx units for* 5-methoxyindolacetic acid *and < xx units for* 5-MeO-DMT-N-Oxide

Programming notes: *Values below LLOQ are shown as* BLQ. Check LLOQ value in final PK spreadsheet for each analyte.

Template L_PD1_PG

Listing 16.2.x.xx Listing of Stanford Expectation of Treatment Scale

Treatment	Patient	Planned Relative Time	Date/Time	Positive expectancy	Negative expectancy
		Time 1	26SEP2012:09:57	x	x

Template L_PD2_PG

Listing 16.2.x.xx Listing of Mystical Experience Questionnaire (MEQ-30)

Treatment	Patient	Planned Relative Time	Date/Time	Mystical Subdomain	Positive Mood Subdomain	Transcendence of Time and Space Subdomain	Ineffability Subdomain	Total MEQ Score
		Time 1	26SEP2012:09:57	x	x	x	x	x

Template L_PD3_PG

Listing 16.2.x.xx Listing of Ego Dissolution Inventory (EDI)

Treatment	Patient	Planned Relative Time	Date/Time	Question 1	Question x	Total EDI Score	Comment
		Time 1	26SEP2012:09:57	x			

Programming note: Total EDI Score only required for EDI

Template L_PD4_PG

Listing 16.2.x.xx Listing of Stanford Expectation of Treatment Scale (SETS)

Treatment	Patient	Planned Relative Time	Date/Time	Positive expectancy	Negative expectancy	What treatment are you going to receive?	Specific benefits you expect to receive?	Specific harms or negative side-effects you think may occur?	Have you ever received this treatment?
		Day -12	26SEP2012/09:57	x.xx	x.xx	xxxxxxxxxx	xxxxxxxxxxx	xxxxxxx	No

Template L_PD4a_PG

Listing 16.2.x.xx Listing of Montgomery-Åsberg Depression Rating Scale (MADRS)

Treatment	Patient	Planned Relative Time	Date/Time	Total MADRS Score	Etc.
		24 H	26SEP2012/09:57	x	

All questionnaire programming notes: Include columns for all scores (total and/or average score) for all questionnaires (where applicable) as described in Appendix A.

Template L_PD5_PG

Listing 16.2.x.xx Listing of 5-Level EuroQol 5-Dimension (EQ-5D-5L)

				Mobility					Self-care		
Treatment	Patient	Planned Relative Time	Date/Time	I have no problems in walking about	I have slight problems in walking about	I have moderate problems in walking about	I have severe problems in walking about	I am unable to walk about	I have no problems washing or dressing myself	I have slight problems washing or dressing myself	etc
		24 H	26SEP2012/09:57	x	x	x	xx		x	x	

Programming notes: *Continued with all Items assessed including the VAS "How good or bad your health is today (mm)" and time points.*

Template L_PD6_PG

Listing 16.2.x.xx Listing of Timeline Follow-Back (TFLB)

Treatment	Patient	Longest continuous number of abstinence (days)	Max number of standard units of alcohol consumed on any one day					Number of Heavy Drinking Days (HDD)					Number of days after dosing to first drink	Number of days after dosing to first HDD	Average number of standard units of alcohol consumed per week				
			85 Days Prior Day-3	Day 14	Day 28	Day 56	Day 84	85 Days Prior Day-3	Day 14	Day 28	Day 56	Day 84			85 Days Prior Day-3	Day 14	Day 28	Day 56	Day 84
		x	x	x	x	x	x	x	x	x	x	x			x	x	x	x	x

listing continued

Treatment	Patient	Percentage of Heavy Drinking Days (PHDD)					Percentage of Drinking Days (PDD)					Mean Units per Day (UPD)					Abstinence: Percentage of Abstinent Days (PAD)				
		85 Days Prior Day-3	Day 14	Day 28	Day 56	Day 84	85 Days Prior Day-3	Day 14	Day 28	Day 56	Day 84	85 Days Prior Day-3	Day 14	Day 28	Day 56	Day 84	85 Days Prior Day-3	Day 14	Day 28	Day 56	Day 84
		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Note: 85 Days Prior Day -3 = 85 Days Prior Day -3 (or start of detox)

Template L_PD7_PG

Listing 16.2.x.xx Listing of Alcohol Craving Questionnaire (ACQ)

Treatment	Patient	Planned Relative Time	Date/Time	Question 1	Question 2	Etc.
		Time 1	26SEP2012:09:57	x		

Template L_PD8 _PG

Listing 16.2.x.xx Listing of Clinical Global Impression-Severity (CGI-S)

Treatment	Patient	Planned Relative Time	Date/Time	Considering your total clinical experience with this patient population, how ill is the patient at this time?
		Time 1	26SEP2012/09:57	0

Programming notes: For PGIC use "Since the start of the study, my overall status is"

Template L_PD9_PG

Listing 16.2.x.xx Listing of Clinical Institute Withdrawal Assessment for Alcohol- Revised (CIWA-Ar)

Treatment	Patient	Planned Relative Time	Date/Time	Nausea and vomiting	Tremor	Paroxysmal Sweats	Etc.
		Time 1	26SEP2012:09:57	x	x	x	x

Template L_AE1_PG

Listing 16.2.x.xx Listing of all adverse events

Treatment	Patient	System Organ Class* / Preferred Term/ Verbatim Text	Outcome/ Onset Date/Time/ Resolved Date/Time/ Duration	Study Day Started/ Time Since Last Dose	Severity/ Serious/ Withdrawal/AESS/ AESI	Frequency/ Action Taken (1)/ Other Action Taken	Related to Study Drug/ Treatment Emergent?
Treatment 1	1001	Gastrointestinal Disorders / Intestinal Spasm / Entero-spasm	Resolved/ 24SEP2003 13:05/ 27OCT2003 7:50/ 34d 4h 5m	Day x/ 10d 7h 3m	Mild/ No/ Yes	Intermittent/ Dose not changed/ None	Possibly/ Yes

(1) Action Taken with Study Treatment
*Coded using MedDRA vXX.X
AESS = Adverse event of special situation
AESI = Adverse event of special interest

Programming notes: *For the listing of "other significant AEs" include (from ICH E3) AEs leading to withdrawal, AEs leading to dose reduction (including drug withdrawn, interrupted, reduced or similar) and AEs with AEOSE=Y. If AEOSE has not been collected then use "Otherwise significant" in the CRF.*

Template L_LB1_PG

Listing 16.2.x.xx Listing of post dose clinically significant abnormal chemistry laboratory values

Treatment	Patient	Laboratory test (units)	Planned Relative Time	Date/Time	Value	Clinically Significant?
Treatment 1	1001	XXX	Time 1	01JAN2002/13:34		
			Time 2	01APR2002/09:22		Y

Programming notes: *Lists only patients with clinically significant post-dose results. Alcohol biomarkers, include CDT and Urine EtG*

Template L_VS1_PG

Listing 16.2.x.xx Listing of vital signs of potential clinical importance

Treatment	Patient	Planned Relative Time	Date/Time	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Etc (units)
		24 H	26SEP2012:09:57	63	148*	

* Value of potential clinical importance

Template L_VS2_PG

Listing 16.2.x.xx Listing of clinically significant vital signs

Treatment	Patient	Planned Relative Time	Date/Time	Vital Sign Finding	Comment on Clinical Significance

Programming notes: *Lists only values with abnormal CS*

Template L_VS3_PG

Listing 16.2.x.xx Listing of peak vital signs data

Treatment	Patients	Planned Relative Time	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)
		Predose	160	148	50
		Day 0, Postdose	163	148	55

Programming notes: *Continued with all treatments and subjects. List only the maximum value*

Template L_EG1_PG

Listing 16.2.x.xx Listing of QTcF values of potential clinical importance

									QTcF (msec)	
Treatment	Patient	Planned Relative Time	Date/Time	Heart Rate (bpm)	PR Int. (msec)	QRS Dur. (msec)	QRS Axis (deg)	QT Int. (msec)	Observed	Change from Baseline
		24 H	26SEP2012:09:57	63	148	78	50	390	396	-6.5

* Value of potential clinical importance

Template L_EG2_PG

Listing 16.2.x.xx Listing of abnormal ECG findings

Treatment	Patient	Planned Relative Time	Date/Time	ECG Finding	Comment on Clinical Significance

Programming notes: *Lists only abnormal values or values with comment on ECG result*
ECG Finding contains Physician's Opinion from CRF and relates to whole trace (not individual parameters), e.g. Normal, Abnormal - NCS or Abnormal - CS

Template L_EG3_PG

Listing 16.2.x.xx Listing of abnormal cardiac telemetry findings

Treatment	Patient	Start Date/Start Time	End Date/End Time	Telemetry Finding Abnormal - CS	Comment on Clinical Significance

Programming notes: *Lists only abnormal values or values with comment on telemetry result. Telemetry findings will be in the form Normal, Abnormal - NCS or Abnormal - CS*

Template L_PE1_PG

Listing 16.2.x.xx Listing of abnormal physical examination findings

Treatment	Patient	Planned Relative Time	Date	Site	Details

Programming Notes: *List only findings with an 'abnormal' result. Details contains Details concatenated with NCS or CS*
If patients have multiple abnormal sites at a given time, create a separate row for each site.

Template L_NSE1_PG

Listing 16.2.x.xx Listing of abnormal nasal site and throat examination findings

Treatment	Patient	Planned Relative Time	Date/Time	Site	Details	Irritancy Score

Programming Notes: *List only findings with an 'abnormal' result. Details contains Details concatenated with NCS or CS*
If patients have multiple abnormal sites at a given time, create a separate row for each site.

Template L_CSS_PG

Listing 16.2.x.xx Listing of positive columbia-suicide severity rating scale data

Treatment	Patient	Planned Relative Time	Date/Time	Question	Category	Result

Template L_RDQ_PG

Listing 16.2.x.xx Listing of readiness for discharge questionnaire (RDQ)

Treatment	Patient	Planned Relative Time	Start Date/Time	End Date/Time	Question	Result
	1001	Time 1	26SEP2012:09:52:20	26SEP2012:09:54:20	The patient is fully responsive	No
					The patient is fully responsive	Yes
					Acute psychedelic effects have subsided	Yes
					The patient is fully orientated	Yes
					Blood pressure/pulse rate are normal	Yes
					Patient has stable gate can walk safely	Yes
					Side effects are mild/moderate intensity	Yes
					No acute suicidal ideations/intentions	Yes
					Feelings of being overwhelmed have gone	Yes
					The patient is now safe to be discharged	Yes
					Time to discharge (hours)	2.3

Note: Time to discharge is defined as time when all criteria are met

Programming Notes: *Continued with all questions. Calculate time to discharge from the end time and report as last row*

Template L_ReAQ_PG

Listing 16.2.x.xx Listing of re-activation questionnaire (ReAQ)

									Functional Impact			
Treatment	Patient	Planned Relative Time	Date/Time	Occurrence	Date of event?	No. of Days after dose	No. of Re-activations	Emotional Valence	Work	Social Life	Family Life	Narrative
				Yes	26SEP2012	5	2	Mostly Positive	Mild	Mild	Moderate	xxxx
				No								

19.3 Table of footnotes for data display specifications (questionnaires only)

Listing/Table Number	Description	Footnotes
16.2.6.2	Listing of Stanford Expectation of Treatment Scale	SETS is a 10 item scale with 6 items used to calculate expectancy
16.2.6.3	Listing of Mystical Experience Questionnaire (MEQ-30)	Total MEQ-30 Score = (Mystical Subdomain + Positive Mood Subdomain+ Transcendence Subdomain + Ineffability Subdomain) / 4 A 'complete mystical experience' is defined as a patient scoring 3 or more on each of the four subdomains.
16.2.6.4	Ego-Dissolution Inventory (EDI)	The EDI is an 8-item measure which will be used to measure the acute ego dissolution experience during dosing using visual analogue scale (VAS) from 0 ('No, not more than usually') to 100 ('Yes, entirely or completely'). Total score is calculated as mean of all 8 items.
16.2.6.12	Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar)	The maximum score is 67; mild alcohol withdrawal is defined by a score ≤10, moderate by scores 11 to 15, and severe by any score ≥16.

Appendix A: Pharmacodynamic analysis

1 Montgomery and Asberg Depression Rating Scale (MADRS)

1.1 Introduction

The Montgomery–Asberg Depression Rating Scale (MADRS) consists of 10 items evaluating core symptoms of depression. Nine of the items are based upon patient report and one is on the rater's observation during the rating interview. Items are rated between 0-6 (0=no abnormality, 6=severe).

1.2 Analysis and reporting

The total score is calculated by adding the scores from the 10 items. The overall score ranges from 0 to 60. Higher scores suggest greater levels of depression. Total scores will not be calculated where there is a missing data. The individual questions will also be reported.

2 Mystical Experience Questionnaire (MEQ-30)

2.1 Introduction

The Mystical Experience Questionnaire (MEQ-30) was developed by Pahnkein 1963 as a tool for the evaluation of single mystical experiences occasioned by hallucinogens.
The MEQ-30 consists of 30 scale items (0- none/not at all to 5- extreme (more than any other time in my life and stronger than 4).

2.2 Analysis and reporting

Factor scores are computed by calculating the mean response to the following items:

- Mystical items are: 4, 5, 6, 9, 14, 15, 16, 18, 20, 21, 23, 24, 25, 26, 28.
- Positive mood items are: 2, 8, 12, 17, 27, 30.
- Transcendence items are: 1, 7, 11, 13, 19, 22.
- Ineffability items are: 3, 10, 29.

The MEQ30-total score is computed by taking the mean response to all items.

3 Ego Dissolution Inventory (EDI)

3.1 Introduction

The Ego Dissolution Inventory (EDI) is an self-completed questionnaire designed to measure ego-dissolution.

3.2 Analysis and reporting

The EDI consists of 8 visual analogue scale items and a mean score on all 8 items is calculated for a single EDI factor.

4 Timeline Follow-Back (TLFB)

4.1 Introduction

Timeline Follow-back (TLFB) is a calendar-based method used to estimate an individual's daily drinking habits over a given time period.

4.2 Analysis and reporting

The following will be calculated:

Scoring item	Calculation
Longest continuous number of abstinence (days)	Max number of continuous days where units=0
Maximum number of standard units of alcohol consumed on any one day	Max units where units >0
Number of Heavy Drinking Days (HDD)	Total days where units >=9 for men; Total days where units >=7 for women
Percentage of Heavy Drinking Days (PHDD) in 85d prior D-3 (or start of detox) vs PHDD post-dosing measured on d14, d28, d56, d84	% of the number of HDD (see above for definition) for 85d prior D-3 (or start of detox) vs % of the number of HDD D0-D14, D0-D28, D0-D56, D0-D84
Percentage of drinking days (PDD) in 85d prior D-3 (or start of detox) vs PDD post-dosing measured on d14, d28, d56, d84	% of the total days where units > 0 for 85d prior D-3 (or start of detox) vs % of the total days where units > 0 on D0-D14, D0-D28, D0-D56, D0-D84
Mean Units per day (UPD): In 85d prior D-3 (or start of detox) vs UPD post-dosing measured on d14, d28, d56, d84.	(sum of all units)/(85d prior to D-3) vs (sum of all units)/(D0-D14); (sum of all units)/(D0-D28); (sum of all units)/(D0-D56); (sum of all units)/(D0-D84)

Abstinence: Percentage of Abstinent days (PAD) in 85d prior D-3 (or start of detox) vs PAD on d14, d28, d56, d84	% of days where units=0 for 85d prior D-3 (or start of detox) vs % of days where units=0 on D0-D14, D0-D28, D0-D56, D0-D84
Number of days after BPL-003 dosing to first drink	Number of days until units >0 after D0 (dosing)
Number of days after BPL-003 dosing to first HDD (defined by UK government as >=7 units a day for a woman and >=9 units per day for a man)	Number of days until units >=9 (male) or >=7 (female) after D0 (dosing)
Average number of standard units of alcohol consumed per week in 85d prior D-3 (or start of detox) vs post-dosing measured on d14, d28, d56, d84 (and reported referencing UK risk levels)	Average number of standard units of alcohol consumed per week in 85d prior D-3 (or start of detox) vs post-dosing measured on d14, d28, d56, d84

5 Alcohol Craving Questionnaire (ACQ)

5.1 Introduction

Alcohol Craving Questionnaire contains 12 items from the 47 item Alcohol Craving Questionnaire developed to access craving for alcohol among alcohol uses.

5.2 Analysis and reporting

The score for each item is calculated as shown below.

Scoring item	Calculation
Compulsivity - urges and desires in anticipation of loss of control over drinking	SUM(Q4, Q5, Q6)/3
Expectancy - urges and desires to drink in anticipation of the positive benefits of drinking	SUM(Q1, Q2, Q12)/3
Purposefulness - urges and desires coupled with intent and planning to drink	SUM((8-Q3), (8-Q8), (8-Q11))/3
Emotionality - urges and desires to drink in anticipation of relief from withdrawal/negative affect	SUM(Q07, Q09, Q10)/3
General craving index	SUM(Q01,Q02,(8-Q03),Q04,Q05,Q06,Q07, (8-Q08),Q09,ACQ1010,(8-Q11),Q12)/12

6 Craving Visual Analogue Scale (VAS)

6.1 Introduction

Craving Visual Analogue Scale is used to rate patients desire for alcohol.

6.2 Analysis and reporting

Patient will rate their desire to alcohol in a 100 mm line where 0=Not at all and 100=Extremely high. The length in mm will indicate a patients desire for alcohol.

7 Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar)

7.1 Introduction

The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) is a 10-item questionnaire that measures the current degree of severity of an individual's alcohol withdrawal symptoms. Items 1-9 are scored on a scale from 0 to 7, 0 being no symptoms and 7 being severe symptoms. Item 10 is scored on a scale from 0 to 4:

7.2 Analysis and reporting

A total CIWA-Ar score is calculated by summing the scores given for each item. Total score will not be calculated where there is a missing data. The total score and the score for each sub scale will be listed and summarised.

8 Short Inventory of Problems (SIP)

8.1 Introduction

The Short Inventory of Problems is a 15-item questionnaire used to assess participants' perceptions of the adverse consequences of their substance use during 3 months prior to assessment. Each item is rated by the respondent on a four-point Likert-type scale.

8.2 Analysis and reporting

A total SIP score is calculated as the sum of the response from the 15 items. Total score will not be calculated where there is a missing data

9 Stanford Expectations of Treatment Scale (SETS)

9.1 Introduction

As a patient's response to treatment may be influenced by the expectations that the patient has before initiating treatment, the influence of participant expectancy may reduce statistical power in a clinical study. The SETS is a 10-item scale for measuring positive and negative treatment expectancies. SETS is used to improve statistical sensitivity for detecting treatment differences in clinical studies. The first 6 items are rated on a seven-point scoring response scale, where response of "Strongly Disagree" = 1, "Moderately Disagree" = 2, "Slight Disagree" = 3, "Neither Agree Nor Disagree" = 4, "Slightly Agree" = 5, "Moderately Agree" = 6, and "Strongly Agree" = 7.

9.2 Analysis and reporting

The SETS items are grouped into the following scales with total scores calculated as the mean of the ratings within each scale. Questions 7 to 10 will also be listed.

Scale	**Question number**
Positive expectancy	1, 3, 5
Negative expectancy	2, 4, 6

Appendix B: Sample page layout

Beckley Psytech Ltd : BPL-003-203 Page x of y*

Population: [Pop]

Table *[number] [title]*

Column headers

Main body of output

Source: Listing *[16.2.xx]*

Footnotes about the table or listing text go here.

Program: *[Prog Name]* [Date] HMR 22-502

Produced By: *[Username]*

*y = last page of individual output

Font size will be Arial 9.5pt. The following margins will be used: Left: 1", Right: 1", Top: 1", Bottom: 1"