Dose-finding Study for the Combination of DMT and Harmine in Healthy Subjects (DHT-P)

Statistical Analysis Plan (SAP)

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Note: *Italicized* text within this document has been taken verbatim from the Protocol.

1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
BASEC	Begleitete Dokumentation von klinischen Studien (“Accompanied documentation of clinical studies”)

3. INTRODUCTION

Understanding the neurodynamics of emotional and behavioral states through pharmacological stimulation with psychoactive compounds that modulate specific neurotransmitter systems in the brain represents a current research priority in cognitive and affective neuroscience. The endogenous neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) seems to be crucially involved in the regulation of mood and social cognition. Hence, serotonergic psychoactive compounds have been used to investigate the pharmacological underpinnings of emotional processing, social cognition and empathy in human subjects. Psilocybin, LSD, DMT and MDMA provide valuable tool compounds for the safe investigation of serotonergic neurotransmission, brain function and the association of these neural changes with emotional and cognitive states (1-3). *In recent years, psychedelic compounds such as psilocybin, LSD, ayahuasca and the dissociative anesthetic ketamine have been used in clinical and non-clinical trials to investigate the underlying neural mechanisms of action and to explore their efficacy in the treatment of affective disorders such as major depressive disorder (MDD), anxiety disorders, substance use disorders (SUD), and post-traumatic stress disorder (PTSD)* (2, 4, 5). *As a 5-HT2A-receptor agonist, DMT needs to cross the blood-brain-barrier (BBB) in order to evoke its psychotropic effects on the human psyche. This is achieved by parenteral administration either via smoking/vaping the substance, or by direct intravenous administration into the blood stream* (6-8). *However, DMT is not able to evoke noticeable effects by stand-alone oral administration* (8, 9). *This is due to the intense first pass-effect occurring in the gastro-intestinal tract by monoamine oxidase (MAO)* (8). *Urine analysis after intravenous administration of DMT to volunteers yielded indole-3-acetic acid (IAA) as the main metabolite of DMT, which is the oxidative deamination product of the examined drug* (6). *Further evidence for the involvement of MAO in the metabolism of DMT is given by the pharmacology of ayahuasca, as the traditional brew consists also of Banisteriopsis caapi, the ayahuasca vine that contains high concentrations of the β-carboline alkaloids harmin, harmaline, and tetra-hydroharmine. All of those alkaloids were shown to be reversible MAO-A inhibitors and are necessary to facilitate the psychoactive effects of ayahuasca* (10-13). *MAO however, is not the only enzyme metabolizing DMT in the human body, as urine samples were found to contain DMT-N-oxide (DMT-NO) in significant concentrations, besides DMT and IAA* (14). *When DMT is administered alone, urine analysis 24h after intake resulted in a composition of DMT and its two main metabolites DMT-NO and IAA in a ratio of 0.04%, 3.05% and 96.91% respectively* (8).

The goal of this clinical trial is to compare corresponding inter- and intraindividual pharmacokinetic and pharmacodynamic profiles of DMT and the MAO-A inhibitor harmine, including assessments of safety & tolerability.

3.1. Study Design

This is a single-blind, randomized, two-arm, dose-response study of DMT and harmine in healthy subjects.

N = 16 healthy female and male subjects (25-45 y) with no current or previous history of neurological or psychiatric disorder and no first-degree relatives with history of Axis-I psychiatric disorder will be recruited by medical screening. In this open-label pilot study, acute subjective effects and blood samples following the administration of escalating doses of DMT and harmine as a sublingual single preparation are measured. Additionally, on the fourth test day participants will receive either DMT or harmine only as a sublingual preparation according to their arm allocation. The study will be conducted at the Psychiatric University Hospital Zurich (PUK). Study participants will undergo a telephone and medical screening before enrolment to the study. Possible doses for each study day are given in section 3.4. Blood sampling and pharmacokinetic modeling, as well as assessing vital signs and the intensity of subjective effects follows the timeline shown in the figure below. Blood is sampled 15 times over the course of 24 h. Vital signs and the intensity of subjective effects will be monitored throughout the study at baseline, 0, 20, 40, 60, 85, 120, 150, 180, 240, 300, 540, 1440 (= 24h) after administration. This protocol is used for all 6 pilot days. ECG is measured

at baseline, 75, 150, 300, 540, and 1440 min after administration. Body temperature is measured at baseline, 75, 180, 300, 540, and 1440 min after administration. Semistructured interviews will be conducted on the second study day towards the end of the study day. The 'Aliveness' Task will be conducted on the first 3 study days at ~100 min after substance administration. Participants will be released at the end of the study day but will come back the following day for their assessments 24 hours after first substance administration.

The daily schedule for study events are displayed in Figure 3. A detailed description of the schedule for the study participation and procedures is provided in the accompanying protocol (BASEC-Nr. 2022-00973).

3.1.1. Initial titration period

We will administer the sublingual formulation with varying fixed starting doses of DMT and harmine and let the study participants increase the total dose of DMT and harmine in 20 minute intervals at fixed increments up to two times. We will test 7 different dosing conditions with varying DMT:harmine ratios during the first 4 days (see figure 1). The tested ratios range between 0-120 mg DMT and 0-180 mg harmine. The dose ratios will be administered in a sequential order with two different sequences in two arms, and the DMT or harmine only condition will be tested on the fourth study day; this is done to further clarify if DMT alone is capable of inducing its effects with routes other than intravenous administration or inhalation. The DMT/harmine only condition is the only one that is exclusive for one of the two study arms. The rationale behind this dosing scheme is to find the optimal dose of harmine and DMT independently of each other by taking account for order/PD habituation and linear/non-linear drug-drug-interaction effects and to establish the optimal dosing for the future studies based on PK/PD analytics.

3.1.2. Non-identical cross-over period

A non-identical cross-over paradigm will be applied on days 5 and 6. This scheme will allow us to explore DMT/harmine in additional combinations which were explored in the initial titration phase so that all individuals in both treatment arms have been exposed to all combinations, except for the DMT-only and Harmine-only conditions which are unique to each arm. The timeline for this study is shown in figure 2.

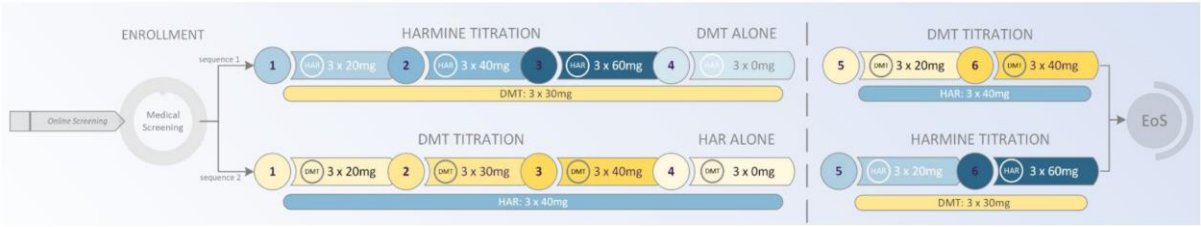

Figure 1. Dose ratios for the dose-finding study. The sublingual formulation is administered in a ratio-varying manner on six study days in two arms that differ in the order of substance administrations (equivalent to a cross-over design). On the 4th study day, participants will either receive DMT or harmine only, depending on the arm they are allocated to.

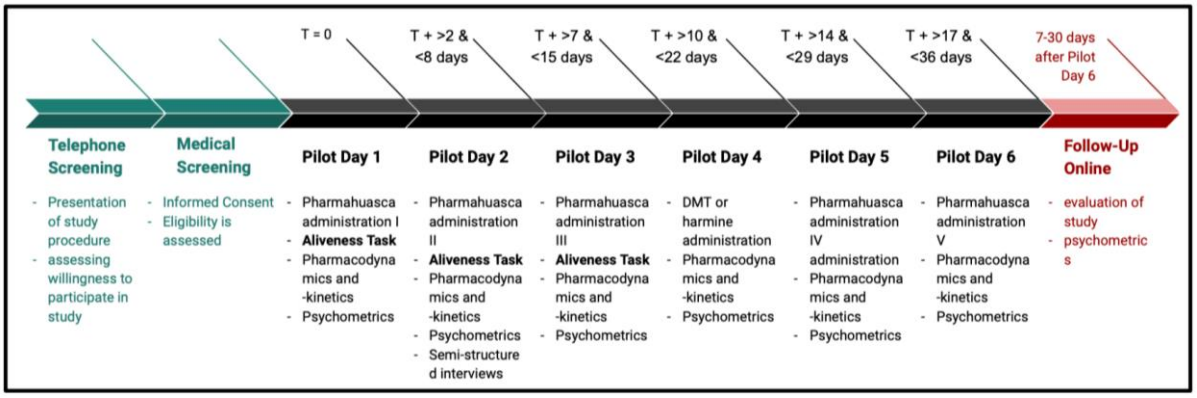

Figure 2. Study flow chart for the dose-finding study.

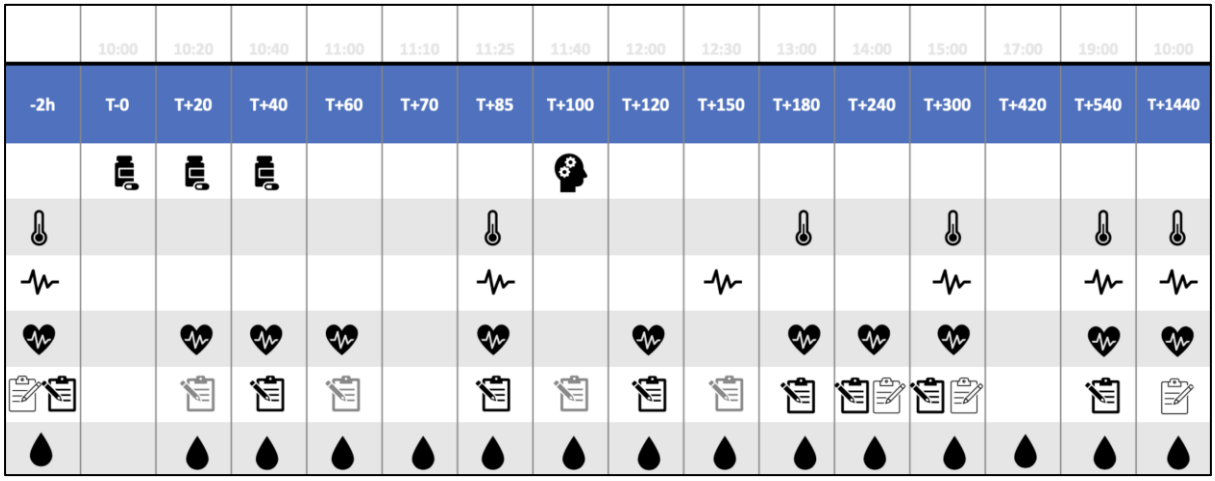

Figure 3. Timeline of drug administration and assessments for each study day.

2.2 Study Objectives

2.2.1 Primary Objective

- To determine the safety and tolerability of various dose combinations of a DMT/harmine formulation in healthy subjects.

2.2.2 Secondary Objectives

- To characterize the PK of DMT in plasma and urine following oral administration of escalating single oral doses to healthy subjects.
- To characterize the PK of harmine in plasma and urine following oral administration of escalating single oral doses to healthy subjects.

2.2.3 [redacted]

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3. HYPOTHESES AND DECISION RULES

3.1. Statistical Hypotheses

No formal statistical tests are anticipated, unless adequate conditions for within-subject analyses are met.

3.2. Statistical Decision Rules

If protocol adherence is sufficient for within-subject statistical tests to be valid and the collected data from the study prove suitable for such analysis, a mixed-effects model would be applied. This model would utilize subjective effects and DMT AUC as dependent variables.

4. ANALYSIS SETS

4.1. Full Analysis Set

In general, the full analysis set is composed of all randomized subjects, following the intention-to-treat (ITT) principle. The ITT principle includes all subjects in the analysis based on their randomized treatment assignment, regardless of whether they received the treatment, completed the study, or adhered to the protocol. Analysis sets for PK, pharmacodynamic, safety, and the highest dose condition data are defined in Sections 4.2, 4.3, 4.4, and 4.5.

4.2. Pharmacokinetic Analysis Set

4.2.1. Concentration Analysis Set

The PK concentration population is defined as subjects treated who were administered all three doses for at least one dose condition.

4.2.2. Parameter Analysis Set

The PK parameter population is defined as subjects treated who were administered all three doses and have at least one of the PK parameters of interest for at least one dose condition.

4.3. Pharmacodynamic Analysis Set

The pharmacodynamic analysis population is defined as subjects who were administered all three doses and have at least one of the pharmacodynamic parameters of interest for at least one dose condition.

4.4. Dose Interruption Analysis Set

The Dose Interruption population is defined as subjects treated who were administered two out of the three doses per dose combination.

4.4.1. Pharmacokinetic Analysis Set

4.4.1.1 Concentration Analysis Set

The Dose Interruption PK concentration population is defined as subjects treated who were administered only two doses for at least one dose combination.

4.4.1.2 Parameter Analysis Set

The Dose Interruption PK parameter population is defined as subjects treated who were administered only two doses for at least one dose combination and have at least one of the PK parameters of interest.

4.4.2. Pharmacodynamic Analysis Set

The Dose Interruption pharmacodynamic population is defined as subjects treated who were administered only two doses for at least one dose combination and have at least one of the pharmacodynamic parameters of interest.

4.5. Safety Analysis Set
Subjects who receive at least one dose of study medication for any dose combination will be included in the safety analyses and listings.

4.6. Treatment Misallocations
All analyses will be performed as “per protocol” and will not include data from subjects who are randomized but not treated.

If a subject takes a treatment that is not consistent with the treatment they are randomized to, for example takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they received for all safety, PK and pharmacodynamic analyses, where applicable.

4.7. Protocol Deviations
Subjects who experience events that may affect their PK profile (e.g., vomiting) may be excluded from the PK analysis if a clear rationale thereof is documented. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

4.7.1. Deviations Assessed Prior to Randomization
At screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 – Section 4.2 of the protocol.

4.7.2. Deviations Assessed Post-Randomization
Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

5. ENDPOINTS AND COVARIATES
Subjects who receive at least one dose of randomized study IMP and have a baseline and at least one post-baseline measurement (after taking randomized study medication) will be included in the data analyses. Baseline is defined as the last pre-dose measurement from each measurement day.

5.1. Primary Endpoint(s)
- Pharmacokinetic parameter "Cmax": Dose-dependent changes in Cmax of several doses of combined DMT & Harmine.
- Pharmacokinetic parameter "Area under the curve (AUC)": Dose-dependent changes in AUC of several doses of combined DMT & Harmine.
- Pharmacokinetic parameter "T1/2": Dose-dependent changes in T1/2 of several doses of combined DMT & Harmine.
- Incidence of Treatment-Emergent Adverse Events: Dose-dependent changes in incidence of adverse drug reactions.
- Blood count (Lab biochemistry): Changes from baseline in blood count.
- Clinical chemistry (Lab biochemistry): Changes from baseline in any clinical chemistry parameter with potential clinical relevance.
- Blood coagulation (Lab biochemistry): Changes from baseline in blood coagulation.
- QT interval (12-lead Electrocardiogram [ECG]): Dose-dependent changes of QT intervals assessed by clinical 12-lead ECG).
- Blood pressure: Dose-dependent changes in systolic and diastolic blood pressure.
- Heart rate: Dose-dependent changes in heart rate.

- Temperature: Dose-dependent changes in body temperature (in °C).
- Genotyping: Collection of saliva-samples to determine genetic polymorphisms.
- Subjective effects: Dose-dependent changes in trajectories of subjective effects.

5.2. Secondary Endpoint(s)

- Aliveness - Behavioral Task: Validated instrument developed to assess dose-dependent changes in perceived aliveness.
- Heart-rate-Variability, Physical Activity, Sleep Patterns: Wearable device for continuous sensor assessments.
- Heart-rate-variability: Occurrence of dose-dependent changes in heart-rate-variability assessed by a wearable device.
- Physical Activity: Occurrence of dose-dependent changes in physical activity assessed by a wearable device.
- Sleep Patterns: Occurrence of dose-dependent changes in sleep patterns assessed by a wearable device.

5.3. Pharmacokinetic Endpoints

Blood samples for PK analysis of DMT and harmine will be taken according to the study design given in the protocol.

The following PK parameters will be calculated for DMT and harmine (if possible) from the plasma concentration-time data as decided by the pharmacokineticist.

5.3.1 Cmax

Definition: Concentration-time profile from time zero to the time of the last quantifiable concentration.

Method of determination: Observed directly from the data.

5.3.2 AUC

Definition: Concentration-time profile from time zero to the time of the last quantifiable concentration

Method of determination: Linear/Log trapezoidal method.

5.3.3 T 1/2

Definition: Terminal elimination half-life.

Method of determination: $(Ln2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression. This parameter can be calculated if permitted by the available data.

5.3.4 Reporting pharmacokinetic data

The PK parameters will be summarized descriptively by dose combination condition in accordance with the Standard Operating Procedures (SOP).

Individual and average blood plasma concentrations for DMT and harmine will be plotted separately against sampling time points for each dose combination. These plots will be used to help understand the relationship between the plasma PK parameters and dose. Additional PK analyses may be performed if deemed appropriate.

5.4. Safety Endpoints

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- Adverse events
- Laboratory data
- Vital signs (blood pressure, heart-rate)
- ECG results

5.4.1. Adverse Events

Adverse events (AEs) will be recorded as defined in Section 6.2 of the protocol.

5.4.2. Laboratory Safety Tests

Safety laboratory tests will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will consider whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

5.4.3. Vital Signs

Single supine measurements will be taken at times detailed in Sections 3.2-3.3 of the protocol.

The following vital signs endpoints will be determined:

- The maximum decrease and increase from baseline (pre-dose) over all measurements taken post-dose for supine systolic and diastolic blood pressures.
- The maximum decrease and increase from baseline (pre-dose) over all measurements taken post-dose for body temperature.

The maximum increase from baseline (eMAX) will be calculated by first subtracting the baseline value from each post-dose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a subject does not show an increase. In such an instance, the minimum decrease should be taken.

Similarly, the maximum decrease from baseline (eMIN) will be determined by selecting the minimum value of the changes from baseline. In cases where a subject does not show a decrease, the minimum increase should be taken.

5.4.4. ECG

ECGs will be recorded at multiple timepoints throughout the acute measurement period, starting from the pre-dose baseline of each study visit when doses are administered, as detailed in Section 3.3 of the protocol.

The QT, QTc, PR, RR, QRS and heart rate will be recorded at each assessment time.

If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

$$QTcF = QT / (RR)^{1/3} \quad \text{where RR = 60/HR (if not provided)}$$

If not supplied, QTcB will be derived using Bazett's heart rate correction formula:

$$QTcB = QT / (RR)^{1/2} \quad \text{where RR = 60/HR (if not provided)}$$

The maximum absolute value (post-dose) and the maximum increase from baseline for QTcF, QT, heart rate, PR and QRS, will be determined over all measurements taken post-dose for QTcF, PR and QRS.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each post-dose measurement to give the change from baseline. The maximum of these values over

the respective period will then be selected, except in the case where a subject does not show an increase. In such an instance, the minimum decrease should be taken.

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5.5.2. [redacted]

[redacted]

5.5.3. [redacted]

[redacted]

6. HANDLING OF MISSING VALUES

A designated biostatistician may apply multiple data imputation techniques, including pairwise deletion and imputation, and compare the approaches for quality control purposes at their own discretion.

6.1. Concentrations below the Limit of Quantification

In summary statistics for pharmacokinetic assayed values below the lower limit of quantification (LLOQ) will be set to zero. The imputations (e.g., ½ LLOQ) may be considered in other analyses if deemed appropriate. Values below the LLOQ will be reported as "<LLOQ" where LLOQ will be replaced with the numerical value for the lower limit of quantification. The LLOQ for various PK and concentrations will be noted in all tables and listings.

6.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if one of the following cases is true:

1. A concentration has been collected as ND (i.e., not done) or NS (i.e., no sample),
2. A relevant deviation in sampling time (as defined in ICH guideline M4S(R2)) is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

6.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (i.e., not calculated). Note: NC values will not be generated beyond the day that a subject discontinues.

In summary tables, statistics will be calculated by setting NC values to missing, and statistics will be presented for a particular dose with 3 evaluable measurements.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1. Sample Size Determination

Given the relatively high PK variability observed in a previous bioavailability study employing another route of administration, N=8 is considered the minimum acceptable sample size, and N=12 would be sufficient as defined by clinical and analytical standards (EMA: Note for guidance on the investigation of bioavailability and bioequivalence, CPMP/EWP/QWP/1401/98). In preparation N=4 dropouts, we determined that N=16 subjects is sufficient.

7.2. Statistical Methods

Given the exploratory nature, descriptive statistics and graphic visualizations will be provided. No formal statistical hypothesis testing is anticipated.

7.3. Statistical Analyses

7.3.1. Pharmacokinetic Analysis

7.3.1.1. Pharmacokinetic Parameters

To assess the pharmacokinetics of DMT/harmine dose formulations, the PK parameters detailed in Section 5.3 will be listed and summarized for subjects in the PK analysis sets (as defined in Section 4.2 and Section 4.4.1). Missing values will be handled as detailed in Section 6. Each PK parameter will be summarized by dose combination, and will include the set of summary statistics as specified in the table below:

Table 1. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC, Cmax	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T ½	N, median, minimum, maximum.

There will be 1 summary table presenting all PK parameters. This will include data from all dose combinations. The treatment subheading will include the dose condition and dosing regimen information.

To assess the relationship between the PK parameters and dose, dose normalized AUC and Cmax will be plotted against dose.

If the conditions listed in Section 3.2 are met, AUC (if data permit) and Cmax will be analyzed using mixed-effects models for all administered dose combinations. The purpose of these analyses is to obtain estimates of the intra-subject variation to assist in the planning of future studies.

Supporting data from the estimation of 'T ½' will be listed by analyte where applicable: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC based on extrapolation, and the first, last, and number of time points used in the estimation of kel. This data may be included in the clinical study report.

Presentations for DMT and harmine concentrations will include:

- concentration data according to dose conditions, number of doses administered, and nominal time points for individual subjects in the form of a table of concentration data organised to present the effect of dose parameters and time for individuals. Conventional summary statistics for concentration data above the lower limit of quantification will accompany these results.
- plots of median concentrations against nominal time post-dose by dose combination.
- boxplots of dose-normalized AUC and Cmax for each dose combination and number of administered doses per dose combination.
- plots of mean concentrations against nominal time post-dose by dose combination.
- plots of individual concentration against actual time post-dose by dose combination.
- plots of individual concentration by subject against actual time post-dose.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

7.4. Safety Analysis

For each dose combination a set of summary tables split by treatment will be produced separately to evaluate the safety/tolerability of each DMT/harmine dose combination.

No formal analyses are planned for safety/tolerability-related data. The other endpoints detailed in Section 5 will be listed and summarized in accordance with sponsor reporting standards, where the resulting data presentations will consist of subjects from the safety analysis set.

7.4.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by treatment.

Data will be reported in accordance with the sponsor reporting standards.

7.4.2. Demographic and Clinical Examination Data

A breakdown of demographic data will be provided for age, race, weight, body mass index and height. Each will be summarized by cohort and overall in accordance with the sponsor reporting standards.

7.4.3. Subject Discontinuation(s)

Subject discontinuations refer to the complete cessation of participation in the study (i.e. dropout), either due to adverse events, personal reasons, or other factors that prevent the participant from attending subsequent dose combination study days. Discontinuations are distinct from declined (intra-visit) dose escalation, where a subject may choose not to receive all dose escalations within a single visit but continues to participate in the study.

Discontinuations due to adverse events, will be thoroughly documented and summarized by treatment group. Data will be reported in accordance with the sponsor reporting standards.

7.4.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

7.4.5. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards.

Mean change from baseline will be plotted against nominal time post dose. On each plot there will be one line for each treatment. Individual plots of changes from baseline will also be produced for each dose combination and total doses per dose combination.

7.4.6. Vital Signs Data

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by treatment and time post-dose, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 5.

Mean changes from baseline for supine systolic and diastolic blood pressure and pulse rate will be plotted against time post-dose. On each plot there will be a separate line for each treatment. Data from all dose conditions will be plotted on the same figure using separate lines for different dose combinations. Corresponding individual plots of changes from baseline will also be produced for each dose combination.

For supine systolic and diastolic blood pressure and pulse rate, the differences between each dose and placebo (dose – placebo) will be summarized (N, mean, 95% confidence interval) and plotted (mean) for each dose combination and timepoint (including baseline).

Maximum absolute values and changes from baseline for vital signs (for supine) will also be summarized descriptively by treatment. Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned post-dose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

7.4.7. ECG Data

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by dose combination and time post-dose using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 5.

Mean changes from baseline in QT, heart rate and QTcF will be plotted against time post-dose. On each plot there will be 1 line for each treatment. Data from all dose combinations will be plotted on the same figure using separate lines for different dose combinations. Corresponding individual plots of changes from baseline will also be produced for each dose combination.

Changes from baseline in QTcF will also be plotted separately against drug concentrations. This will be a scatter plot for all observations where QTcF and drug concentration are recorded. Different symbols will be used for each treatment.

Maximum increase from baseline for QTcF, heart rate, QT, PR and QRS will be summarized by dose combination, according to sponsor reporting standards.

In addition, for QTcF, heart rate and QT, the differences between each dose combination (dose combination 1 – dose combination 2) for each subject will be summarized and plotted (N, mean, 95% confidence interval) for dose combination and timepoint (including baseline).

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by dose combination using categories as defined in Section 8.1 (for QTc these correspond to ICH E14[1]). Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned post-dose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Listings of subjects with any single post-dose value ≥500 msec will also be produced for QTcF.

QTcB will be listed only and not summarized.

7.4.9. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

7.4.10. Screening and Other Special Purpose Data

The additional information which will be acquired during medical screening and pre-baseline measurements are summarised below:

Period	Method	Endpoints
Baseline	Urine samples	Quantification of Amphetamine, Buprenorphine, Benzodiazepine, MDMA, Methamphetamine, Methylphenidate, Opiate/Morphine, Methadone, Oxycodone, Cannabinoids, Tramadol, Spice in urine.
	Urine samples	β-HCG as marker for pregnancy.
Medical Screening	Blood sampling	Electrolytes and kidney function (sodium, potassium, urea, creatinine), liver values (ASAT, ALAT, GGT), thyroid (TSH), inflammation parameters (CRP), glucose.
	Interview	Acquisition of current somatostatus, substance and medication use.
	Interview	Acquisition of current psychostatus.
	Questionnaire	Acquisition of demographics, intelligence, and symptoms checklist.

	Questionnaire	Affective Neuroscience Personality Scale
	Questionnaire	Attachment Style Questionnaire
	Questionnaire	Highly Sensitive Person Questionnaire

8. APPENDICES

8.1. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

QTcF (ms)	450≤ max. <480	480≤ max.<500	max. ≥500
QTcF (ms) increase from baseline	30≤ max. <60	max. ≥60	

Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥140	
QRS (ms) increase from baseline	≥50% increase	

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120
Standing pulse rate (bpm)	min. <40	max. >140

Measurements that fulfill these criteria are to be listed in report.

8.2 [redacted]

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