Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

A randomised, double-blind, placebo-controlled trial to evaluate multiple dose pharmacokinetics, pharmacodynamics, safety, and tolerability of ascending doses of noribogaine in healthy volunteers.

FINAL VERSION 2.0, 19 FEB 2025

Contents

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
AUC	Area Under the Curve
BMI	Body Mass Index
BLQ	Below the Limit of Quantification
C-SSRS	Columbia-Suicide Severity Rating Scale
CFB	Change From Baseline
DBP	Diastolic Blood Pressure
DHP	Data Handling Protocol
ECG	Electrocardiogram
EST	Exercise Stress Test
H	High
HR	Heart rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
L	Low
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MEQ30	Mystical Experience Questionnaire-30
PD	Pharmacodynamic
PK	Pharmacokinetic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to define the variables and provide details of the planned analysis for addressing the objectives of this trial.

The protocol dated 20 Nov 2024, version 6.0 was used to prepare this SAP.

Statistical analysis and reporting will be performed by Richmond as described within this SAP, pharmacokinetic (PK) parameter calculations and PK report will be generated by PharmaKinetic.

Trial OBJECTIVES AND ENDPOINTS

2.1 Trial objectives

Primary

- To determine the pharmacokinetics of noribogaine capsules.
- To establish a PK/PD relationship of noribogaine concentration on change in QT/QTcI interval.

Secondary

- To evaluate the safety and tolerability of noribogaine.

2.2 Endpoints

Primary

- Maximum plasma concentration (C_{max}: Day 1 & Day 8), time to maximum plasma concentration (T_{max}: Day 1 & Day 8), trough concentration prior to next dose (C_{12}, C_{24}), area under the curve at 12 hours and 24 hours ($AUC_{0\text{-}12\ hours}$, $AUC_{0\text{-}24\ hours}$: Day 1 & Day 8, and to infinity ($AUC_{0\text{-}infinity}$), accumulation ratio for AUC, accumulation ratio C_{max}, terminal elimination rate constant (λz), half-life ($t_{½}$), clearance (CL/F) and volume of distribution (Vz/F), whole blood to plasma ratio (1 hour, 2 hours and 6 hours), amount excreted (Ae) (Day 1 & Day 8) and cumulative amount excreted (Cum Ae) (Day 1 & Day 8).
- QT interval corrected for heart rate using individual specific QT interval correction (QTcI) measures (Day 1 & Day 8). Concentration-QTc relationship assessed on placebo-adjusted change from baseline for QTcI ($\Delta\Delta$QTcI) (Day 1 and Day 8).

Secondary

- Adverse events will be elicited by a verbal probe (prior to any trial rating scales). Any events spontaneously reported by the participant or observed by Investigator's staff (physical examinations) will be recorded. Vital signs, clinical laboratory results and ECG abnormalities will be reported as an adverse event if considered clinically significant.

3. TRIAL DESIGN

3.1 Overall Trial Design

This trial will be a randomised, double-blind, sequential-group, multiple-dose, placebo-controlled, dose escalation trial to characterise the pharmacokinetics (PK), pharmacodynamics (PD) and safety of noribogaine in healthy adult participants.

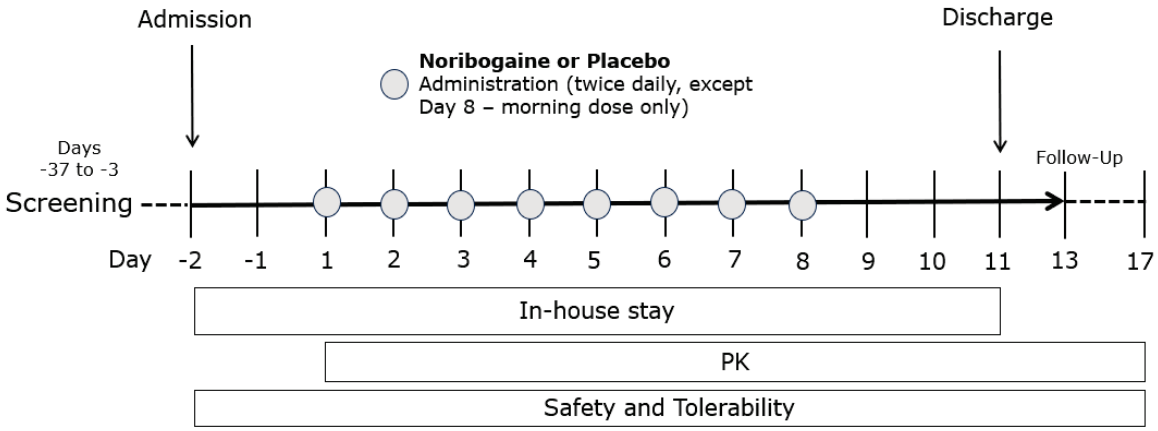
60 healthy participants will be enrolled and randomised to receive either noribogaine or placebo.

The trial will be conducted at a single site in the UK.

The trial consists of a Screening Period (up to 35 days before Admission), followed by an Inpatient Treatment Period. Participants will stay at the trial site for 13 days and will be discharged following completion of the discharge procedures at the end of the period. Participants will return to the trial site 2 to 6 days after Discharge for the follow-up procedures (Follow-up Period).

The overall trial design is depicted in Figure 1.

Figure 1: Study flow chart



Cohorts

Eligible participants will be assigned to one of the four possible cohorts. Each participant will be randomised to receive either noribogaine capsules or placebo orally twice daily for 8 days (except Day 8, morning dose only). Each cohort will consist of 15 participants (12 will be randomised to noribogaine and 3 will be randomised to placebo). The cohorts will be administered the following doses in a sequential fashion as shown in Table 1.

Table 1. Planned Treatment Cohorts and Investigational Medicinal Product (IMP) Administration

Cohort	Number of Participants	Treatment	Planned Dose	Number of Doses
1	12	Noribogaine	1 x 10 mg noribogaine capsule	Study treatments will be administered twice daily to each participant with 240 ml of water. The treatment will be administered for 8 days (with the last dose given on morning of Day 8). The doses will be administered at approximately 12-hour intervals.
	3	Placebo	1 x placebo capsule	
2	12	Noribogaine	1 x 20 mg noribogaine capsule	
	3	Placebo	1 x placebo capsule	
3	12	Noribogaine	1 x 10 mg and 1 x 20 mg noribogaine capsules	
	3	Placebo	2 x placebo capsules	
4	12	Noribogaine	2 x 20 mg noribogaine capsules	
	3	Placebo	2 x placebo capsules	

Four cohorts of 12 participants will be enrolled, with a minimum data requirement of 8 participants dosed in order to conduct the safety review. On completion of the 4 cohorts, the remaining 3 participants from each cohort will be completed as a final group to achieve 4 cohorts of 15, as detailed above.

Periods

Screening

Screening can occur up to 35 days before admission (between Day -37 and Day -3). Each participant will receive verbal and written information regarding the trial and sign the Informed Consent Form (ICF) before any screening procedures can take place. Participants will undergo screening assessments to allow for assessment of safety and the study eligibility criteria. All assessments to be conducted at Screening are found in the Schedule of Assessments (see Protocol).

Admission and Treatment Period

Participants who meet the eligibility criteria following review of all results from the Screening visit will be admitted on Day -2. After eligibility has been established and admission procedures reviewed by a Research Physician, participants will be randomised on Day 1. Dosing and procedures to be conducted are detailed in the Schedule of Assessments in the Protocol.

Follow-up

Following discharge on Day 11, participants will return to the site for a Follow-Up visit between Day 13 and Day 17. During the visit, participants will undergo safety assessments including vital signs and physical examination. Compliance with trial

restrictions will be checked, in addition to the reporting of adverse events and any concomitant medication use.

Participants who withdraw consent before they have completed all trial visits will be encouraged to undergo the follow-up procedures as per the Schedule of Assessments.

3.2 Sample Size

The sample size was selected on the basis of the Sponsor's prior PK studies of similar size in which a dose response in QTc was observed across the expected range of doses and exposures. Using results from a simulation based on data from a prior trial in healthy volunteers, the probability is 95% that a sample size of 12 subjects will produce a two-sided 95% confidence interval with a distance from the mean to the limits that is less than or equal to 0.2 if the population standard deviation is estimated to be no more than 0.2 on the natural log scale. This corresponds to a calculated geometric mean of approximately 80 ng/mL with an upper bound of the 95% confidence interval being less than or equal to 100 ng/mL. The standard deviation is expected to be less than or equal to 20 ng/mL.

3.3 Randomisation and Blinding

All participants will be assigned to a treatment regimen according to a randomisation schedule generated by Pharmacy and/or a Richmond Pharmacology statistician. In each cohort of 15 participants, 12 will be randomised to noribogaine and 3 will be randomised to placebo.

With 4 cohorts and replacement allowance the participants randomisation numbering will be as follows:

- Cohort 1 from 1001 to 1015, replacement subjects from 1101 to 1115
- Cohort 2 from 2016 to 2030, replacement subjects from 2116 to 2130
- Cohort 3 from 3031 to 3045, replacement subjects from 3131 to 3145
- Cohort 4 from 4046 to 4060, replacement subjects from 4146 to 4160

The trial will take place in a double-blinded fashion whereby participants and trial site staff are blinded to the active or placebo treatment. The trial site staff and participants will, however, be aware of the dose level being used.

To maintain blinding, placebos will be used at equivalent timepoints to treatment and participants will receive the same number of capsules with the same appearance.

The pharmacy staff preparing the IMPs will not be blinded to treatment assignment. During the trial, the individual randomisation codes will be kept in the site's clinical trials pharmacy, accessible to the pharmacy personnel only. Upon completion of the trial, after the database lock and after the blind is revealed, the randomisation list will be filed in the Trial Master File.

Sponsor staff involved in clinical decision-making (such as those involved in Safety Review Committee (SRC) decisions) will be blinded to trial treatment. Sponsor staff performing PK analysis will be unblinded but will deliver blinded PK data and reports to the blinded Sponsor and Investigator teams.

3.4 Adaptive Design

The use of an adaptive design has been implemented in areas of this trial with limits specified in the trial protocol section 3.2.

4. STATISTICAL ANALYSES

4.1 General Notes for Statistical Analyses

In general, descriptive statistics for continuous variables will include number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum.

Categorical variables will be summarized using frequency counts and percentages.

For all tables, descriptive statistics for minimum and maximum will be presented with the same decimal digits as the original data, and with 1 more decimal place than the original data for mean and median; SD and SE will be reported with 2 more decimal places than the original data.

The analyses will be presented overall (where appropriate) and by the treatment groups.

All collected data will be presented in by-subject listings. Listings will be ordered by treatment group and subject number and will include all randomised subjects.

Unless otherwise stated, baseline will be defined as the last non-missing value prior to first administration of trial drug. Changes from baseline values will be calculated as the post-baseline assessment value minus the baseline value. Only observed values from scheduled time points will be used to create summary tables, i.e. repeated measurements are made at a time point, the first scheduled value will be used for summary analysis, unless otherwise stated in relevant section of this SAP.

Deviations from the planned analyses will be described in the final clinical study report.

The raw datasets will be converted to SDTM and ADaM formats prior to TFL generation. A submission package will be created, consisting of the SDTM/ADaM datasets, define.xml, annotated CRFs, Reviewer's Guide, and all associated programming scripts.

The TFLs will be generated using SAS version 9.4 or higher, and the pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin version 8.4 or higher.

4.2 Interim Analysis

No interim analysis is planned for this trial.

4.3 Analysis Sets

The analysis of data will be based on different analysis sets according to the purpose of analysis (Table 2). Participant eligibility for each analysis set will be finalised before the DB hard lock. A participant who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of discontinuation.

Table 2: Analysis set

Randomised	All randomised participants. Participants will be analysed according to the intervention to which they were randomised. This population will be used for participants' disposition, demographic characteristics, and baseline characteristic summaries.
Safety	All participants who receive at least 1 dose of IMP. Participants will be classified according to the IMP they received.
PK	All randomised participants who have received at least 1 dose of IMP and have at least 1 evaluable PK parameter.
PD	All randomised participants who receive IMP, that have at least one valid pre-dose ECG assessment and one valid post-dose assessment. An ECG assessment will be considered valid if it is based on at least two evaluable replicates with measurable QT and RR. The analysis set for intensive cardiac assessment will be based on the intersection of the PK set and the ECG set. In addition, participants on placebo will be included with plasma concentrations of IMP set to 0. Individual QTc/concentration pairs will be excluded from this set if the time of ECG and the time of blood sampling are too far apart. Should a participant have no pair of PK and ECG measurements at the same timepoint satisfying this criterion, this participant will be excluded from the set.

Details of ECG/PK allowable time windows extracted from the data handling protocol (DHP) are presented in Appendix 1.

4.4 Subject Disposition

All subjects will be included in the summary of subject disposition. This will present the overall number of subjects, the frequency and percentage of subjects randomised and treated, and who completed or discontinued from the trial, along with reason for discontinuation.

Furthermore, the number and percentage of subjects in each analysis set will be tabulated. Discontinued subjects will be listed. Subject assignment to analysis sets will be listed. Screen Failures will not be listed or included in summary tables.

4.5 Demographic Characteristics

Individual participant demographics (age, gender, ethnicity and race) and body measurement data (height, weight, and BMI) will be listed. These demographic characteristics and body measurements will be summarised by treatment group and overall, using the safety analysis set.

Height will be measured in centimetres and weight in kilograms. BMI will be given in kg/m^2.

Other baseline characteristics such as alcohol breath test, smoking history, exercise test date-time will be listed only.

4.6 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria text will be listed, as well as failed eligibility criteria for each randomised subject, if any.

4.7 Protocol Deviations

The final review of protocol deviations will be performed at the data review meeting prior to database lock. The protocol deviations will be listed.

4.8 Medical and Surgical History

Medical and Surgical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 26.1 (or higher) and listed individually. Surgical history data will be listed separately. Medical and Surgical history data will be summarised using frequency and percentage by system organ class (SOC) and preferred term.

4.9 Trial Drug Administration

Trial drug administration data including treatment received, dose (unit), date and time of administration will be listed by subject.

4.10 Prior and Concomitant Medications

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary version 2024 (or higher) and will be listed individually using safety set. The frequency and percentage of prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical and Preferred Name. Separate tables will be given for prior and concomitant medications.

Prior medications are defined as those for which the end date and time is prior to the date and time of first trial drug administration. Concomitant medications are defined as those with start date and time on or after the date and time of first trial drug administration and those with start date and time prior to the first trial drug

administration but with end date and time on or after the date and time of first trial drug administration.

If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

4.11 Safety Analysis

Safety analyses will be performed on the safety set, unless otherwise stated.

Safety analyses will include an analysis of all AEs, ECGs, clinical laboratory data, vital sign measurements and physical examination results and will be presented using descriptive statistics. No formal statistical analysis will be performed.

4.11.1 Adverse Events

A Treatment Emergent Adverse Event (TEAE) is defined as any adverse event which commences or any worsening of pre-existing conditions after the start of administration of trial drug. AEs with unknown start date/time will be assumed to be treatment-emergent unless the end date/time is known to be before the first administration of trial drug.

AE data will be listed and TEAEs summarised using descriptive statistics: the number (and percentage) of participants who experienced any adverse events (AE) and the number of AE episodes will be summarized for each treatment group. All AEs will be summarized and listed by using the SOC and Preferred Term assigned to the event using the MedDRA dictionary Version 26.1 (or higher). Furthermore, these events will be summarised by the maximum intensity. The number of participants who had drug-related AEs will also be summarised. Any serious adverse events (SAE) and/ or AEs that led to withdrawal will be summarised and listed.

Subjects having multiple AEs within a category (e.g., overall, SOC and Preferred Term) will be counted once in that category. In each table, SOC and Preferred Term will be presented in descending order of overall incidence rate (alphabetical order will be used in case of equal rates).

4.11.2 Laboratory Data

All safety clinical laboratory data, including potassium, magnesium & calcium, will be listed. Laboratory test results will also be compared to laboratory reference ranges and those values outside of the applicable range will be flagged as high (H) or low (L) and as being clinically relevant or not: the number of participants presenting out-of-range and clinically relevant values will be summarised. The quantitative laboratory data, along with changes from baseline will be summarised using descriptive statistics.

The qualitative urinalysis data, urine drug screen, serology and COVID test data will be listed only.

For summary statistics, a lab value with "<" will be replaced with a numeric value by removing the "<" sign. In the listings, the values will be displayed as originally reported by the laboratory.

4.11.3 Vital Signs

Vital signs data (supine SBP, DBP, HR, postural HR, tympanic temperature, oxygen saturation, respiratory rate) will be listed and summarised, along with changes from baseline, using descriptive statistics. Out-of-reference-range values will be flagged as high (H) or low (L) and as being clinically relevant or not by sub-investigators. The number of participants presenting out-of-range and clinically relevant values will be summarised.

Normal ranges for the relevant parameters are presented in Table 3 below.

Table 3: Vital Signs Normal ranges

Parameter	Normal Range
Temperature	35-38°C
Systolic Blood Pressure (Supine)	90–140 mmHg
Diastolic Blood Pressure (Supine)	55–90mmHg
Heart Rate (supine)	55–90 bpm
Postural change in Heart Rate	≤30 bpm
Respiration Rate	8-20 breaths per minute
Oxygen Saturation	93 - 100%

Vital signs performed pre and post exercise Tolerance Test (ETT) will be included within the listings and summary tables with timepoints names as Pre-EST and Post-EST.

4.11.4 Physical Examination

The physical examination will be performed during the trial will be listed only and include an assessment of the following: general appearance, skin, eyes, ears, nose, neck, lymph nodes, throat, heart, lungs, abdomen, musculoskeletal system, neurological system, and extremities.

4.12 Electrocardiogram

4.12.1 Electrocardiogram (ECG)

All un-adjudicated ECG data (PR, QRS, QT, QTcB, QTcF and HR) and overall ECG evaluation will be listed with comments. Out-of-reference-range values will be flagged. ECGs performed pre and post exercise stress test will be included within the un-adjudicated ECG listings with timepoints names as Pre-EST and Post-EST. Unadjudicated ECGs are assessed by sub-investigators during the clinical conduct for safety evaluations, therefore unadjudicated ECGs will be listed only. For ongoing safety assessment on the ward, the last pre-dose ECG timepoint on Day 1 was used as a baseline for real-time evaluation of ECG changes.

Reference ranges for ECG parameters used by sub-investigators during the clinical conduct are presented in Table 4 below.

Table 4: ECG Normal ranges for un-adjudicated ECG evaluations

Parameter	Normal Range
Ventricular Rate (supine)	55-90 bpm
PR Interval	120–200 ms
QRS duration	≤120 ms
QTc	≤450 ms

Adjudicated individual ECG data with triplicate mean values (PR, QRS, QT, QTc and HR) and overall ECG evaluation will be listed with cardiologist evaluations. Out-of-reference-range values will be flagged. ECGs performed pre and post exercise stress test will be included within the un-adjudicated ECG listings with timepoints names as Pre-EST and Post-EST. Cardiologist assessment of ECG parameters are based on the following normal ranges: HR 50-100 bpm; PR 120-220 ms; QRS duration >110 ms; 320 ≤ QTc ≤450 ms.

The below analyses will be performed on the adjudicated ECG set, where triplicates are selected from each time-point, adjudicated and arithmetic mean is calculated from each triplicate.

For summaries by treatment group, all placebo data across cohorts will be pooled.

Adjudicated ECG data and changes from baseline, as well as time matched placebo difference will be summarised using descriptive statistics including 90% CI based on one sample t-tests for absolute values and change from baseline, and on a two sample t-test for the difference to placebo.

The change from baseline (CFB) will be derived using the arithmetic mean value of each timepoint triplicate minus baseline value, where baseline is the arithmetic mean of the pre-dose triplicate ECG values of Day 1. Placebo corrected differences from baseline will be calculated as the CFB of each timepoint minus the mean CFB of pooled placebo subjects.

Furthermore, categorical analysis of QTc data will be presented as follows:

- Absolute QTc interval prolongation
  - QTc interval > 450 ms
  - QTc interval > 480 ms
  - QTc interval > 500 ms
- Change from baseline in QTc interval
  - QTc interval increases from baseline > 30 ms
  - QTc interval increases from baseline > 60 ms
- Fulfilling both, absolute QTc values >480 ms and QTc >30 ms;

Additional categorical analysis will be presented as follows:

- Absolute PR values >200 ms, >220 ms, with a pre-dose value below the respective threshold
- ΔPR ≥25%, i.e., post-dose PR outside the range of (0.75, 1.25) of the baseline value
- Absolute QRS duration >110 ms and >120 ms, with a pre-dose value below the respective threshold
- ΔQRS ≥25%, i.e., post-dose QRS outside the range of (0.75, 1.25) of the baseline value
- Absolute HR of <50 bpm or ≥100 bpm, with a pre-dose value below the respective threshold
- Heart rate decrease ≥25% from baseline to a HR of <50 bpm and/or increase ≥25% from baseline to a HR of ≥100 bpm.

Figures

Mean values by treatment group (with placebo pooled across cohorts) and timepoint will be presented graphically for quantitative ECG parameters and their change from baseline. In addition, mean differences to placebo will also be given. Two-sided 90% confidence intervals will be shown for each treatment and timepoint.

4.12.2 ECG Analysis

Intensive cardiac assessments will be performed using food effects on the adjudicated ECGs to establish assay sensitivity. Analysis of drug related QT/QTc interval changes relative to plasma PK concentrations will be conducted on all dose regimens. The principles of this analysis follow the statistical methods described by Garnett et al., 2018[2]. The ECG utilised for this analysis require adjudication by qualified cardiologists in accordance with principles set out in the International Council for Harmonisation (ICH) E14 guideline and subsequent Q&A documents. All ECG recordings are in triplicate and will be compliant with the correct recording and manual adjudication of ECG in thorough QT/QTc studies.

QT Heart Rate Correction

To ensure robustness of the QTcI correction methodology, Holter/telemetry data will be used to extract QT:RR pairs at a wide range of HR values and a sufficient sample size (ideally > 400 pairs). The quality of the extracted ECGs is confirmed by excluding sections with arrhythmia, abrupt changes in heart rate (ideally stable HR for >=1.5 minutes) and artefacts.

QTc will be plotted against RR interval to assess the suitability of the primary correction method.

For each subject, QT:RR pairs from Day -1 will be ranked based on the RR values (slowest to fastest heart rate). The QTcI formula will be derived using only data points with odd ranks (e.g., 1st, 3rd, 5th ranked pairs), while the data points with even ranks (e.g., 2nd, 4th, 6th ranked pairs) will be used to validate the QTcI formula and assess its performance compared to QTcF. This ranking approach ensures a good range of RR values for both determining and validating the QT correction method.

A linear mixed-effects model will be fitted using the data with odd ranks (where QTcI is derived). This model analyses the relationship between log-transformed QT and log-transformed RR, considering both fixed effects (common correction) and random effects (individual variations) for intercept and slope. The individual correction exponent for each subject is then calculated by adding the fixed and the random slope estimated by the model.

To select the best correction method, the mean squared slope criterion (reflecting the average squared difference between predicted and actual values) will be used to assess the goodness-of-fit for each correction method (QTcF and QTcI). More specifically, for each subject, a linear regression of QTc (i.e. one for QTcF and one for QTcI) on RR will be performed based on the data with even ranks and the mean of the squared slopes obtained for each subject will be obtained per correction method. The correction method with the smaller mean squared slopes will be considered more appropriate. Additionally, other visual diagnostic plots will be considered to evaluate the model's assumptions and identify potential outliers.

If, based on the above, QTcF turns out to perform better that QTcI, it will be selected for the analysis.

Baseline

For statistical analysis the average over the three pre-dose ECG values of Day 1 will be used as baseline.

Concentration-QTc analysis

The primary endpoint is defined as the concentration-QTc-model based QTc placebo corrected differences from baseline (ΔΔQTc). ECGs from Day 1 and Day 8 will be used for comparison against baseline. More specifically, a linear mixed effect model relating the change from baseline to the concentration of noribogaine will be fitted. Apart from the concentration, the model will include fixed effects for time (with different levels for Day 1 and Day 8) and treatment ("treatment intercept" with levels active and placebo) and baseline as a covariate. Random effects per subject for the intercept and, if feasible, for the concentration will be included. More specifically, if the model does not converge even after rescaling of the covariates, the random effects for concentration will be removed. If convergence is still not given, the covariance structure may be simplified. If the treatment intercept differs significantly from nought, a nonlinear e-max model may be investigated. Predictions of the effect of noribogaine at the concentrations seen at Tmax will be used to exclude an effect of regulatory concern (ie, a one-sided 95% confidence interval for ΔQTc completely below 10 ms).

Diagnostic plots include the presentation of observed vs. predicted values and the plot of the residuals against the variables in the model as well as against day.

The observed ΔQTc versus concentration will be presented. In addition, a decile plot as described in the White Paper by Garnett et al., [2] will be presented with the partial residual with respect to concentration as dependent and concentration as independent variable.

The appropriateness of the model used will be investigated. In particular, this includes the absence of a delayed C-QTc effect and any relevant deviations from linearity. Presence of a delayed effect will be investigated by a simultaneous plot of ΔΔQTc and the mean concentration, where ΔΔQTc will be derived as described in 4.12.1 above. Note that a delayed effect will be a problem only if the maximum of ΔΔQTc (Umax) is later than the Tmax by 1 hour or more.

Deviations from linearity will be judged from the treatment intercept and the diagnostic plots. A significant treatment intercept will be taken as an indicator for inappropriateness of the model.

Investigation of C-QTc Hysteresis
C-QTc hysteresis will be assessed visually, by presenting plots of mean ΔΔQTc at each post-dose time point and the correcponding noribogaine plasma concentrations, in a temporal order by dose.
The presence of hysteresis may be established if any of the hysteresis plots shows a relevant counterclockwise loop.

Assessment of Secondary ECG endpoints
The ECG Heart rate (HR) and the RR, PR and QRS intervals will be summarised using descriptive statistics and change from baseline analysis.
If a change in HR of 10 bpm or more is observed a formal statistical analysis, including central tendency (by timepoint) and Concentration-HR (C-HR) analysis will be performed.
Overall interpretation (normal/abnormal) and key ECG diagnostics will be summarised by treatment group and presented in shift tables.

Assay sensitivity
The anticipated effect of the meal at 4 hours after drug administration on Days 1 and 8 will be used to show assay sensitivity. This meal is expected to produce a shortening of mean QTc by up to 5 ms at 2 to 4 hours after its ingestion (6h to 8h timepoints). This shortening will be investigated by looking at the contrasts of the time effect comparing the average of the last two preprandial timepoints to each of the 6h to 8h timepoints.

4.12 C-SSRS and MEQ30

The questionnaire data for Columbia-Suicide Severity Rating Scale (C-SSRS) and Mystical Experience Questionnaire-30 (MEQ30) will be listed by treatment and participant. The MEQ30 will be summarised by presenting descriptive statistics for the total score and each of the four factors (Mystical experience, Positive Mood, Transcendence of Time and Space, Ineffability).

4.14 Holter and Telemetry

Holter and telemetry start/end date-times with evaluations will be listed.

4.15 Meals

Meal dates and times with consumption grade will be listed by treatment and subject, ordered by visit and meal times.

4.13 Pharmacokinetic Data

Non-compartmental analysis will be used for estimation of pharmacokinetic parameters.

The following pharmacokinetic parameters will be calculated for noribogaine:

Table 5: Evaluation of Pharmacokinetic Parameters

C_{max}	Maximal plasma concentration (Day 1 and Day 8)
t_{max}	Time at which the maximum plasma concentration occurs (Day 1 and Day 8)
C_{12}, C_{24}	Trough concentration prior to next dose
$AUC_{0\text{-}12}$	Area under the plasma concentration curve from time zero to 12 hours (Day 1 and Day 8)
$AUC_{0\text{-}24}$	Area under the plasma concentration curve from time zero to 24 hours (Day 1 and Day 8)
AUC_{last}	Area under the plasma concentration curve to the last measurable concentration
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time 0 extrapolated to infinite time (Day 1 and 8)
$\%AUC_{extrap}$	Percentage of AUC that is due to extrapolation from t last to infinity $((AUC_{0\text{-}inf} - AUC_{0\text{-}tlast})/AUC_{0\text{-}inf}) \times 100$ (Day 1 and 8)
ARC_{max}	Accumulation ratio based on C_{max} after the first and the last dose (Cmax Day 8/Cmax Day 1)
$ARAUC_{tau}$	Accumulation ratio based on AUC0-tau (AUCtau Day 8/$AUC_{0\text{-}12 \text{ or } 0\text{-}24}$ on Day 1)
$ARC_{trough2}$, $ARC_{trough3}$, $ARC_{trough4}$, $ARC_{trough5}$, $ARC_{trough6}$, $ARC_{trough7}$,	Accumulation ratio based on Ctrough on days 2-7 (Ctrough on multiple dose day/Ctrough on single dose day

λz	Terminal elimination rate constant obtained from linear regression of time vs log-concentration during the terminal elimination phase; using at least three time-points during the terminal elimination phase (Day 1 and Day 8)
$t_{1/2}$	Terminal elimination half-life (Day 1 and Day 8)
CL/F	Plasma clearance after extravascular administration calculated as Dose/AUC_{tau} (Day 8)
Vz/F	Apparent Volume of distribution after extravascular administration; calculated as Dose/(λz *AUC_{0-inf})(Day 1, EDay 8)
Ae	Amount excreted in the urine during dosing interval (mass units)
Cum Ae	Cumulative amount excreted (mass units)
Fe	Fraction of dose excreted in urine over the collection interval; calculated as (cumulative Ae/dose)*100 (%)
Clr	Renal Clearance; calculate as Cum Ae/AUC (over equivalent interval)

Dose normalised PK parameters will be calculated as follows:

Dose normalised C_{max}= C_{max}/Dose

Dose normalised AUC_{0-12}= AUC_{0-12}/Dose

Dose normalised AUC_{0-24}= AUC_{0-24}/Dose

Dose normalised AUC_{0-inf}= AUC_{0-inf}/Dose

The individual plasma concentration data, and the actual time for noribogaine administration and blood sampling will be used in the derivation of the PK parameters. If there is any doubt in the actual time a sample was taken, then the scheduled time will be used.

AUC_{0-t} and AUC_{0-inf} will be calculated using the linear trapezoidal linear/log interpolation method, applying the linear trapezoidal rule up to C_{max} and the log trapezoidal rule for the remainder of the curve. Samples below the lower limit of quantification (LLOQ) prior to the C_{max} will be set to zero. Samples with concentrations below LLOQ after C_{max} will be set to 'missing' and omitted from the analysis. Other pharmacokinetic parameters will be calculated according to standard equations.

In the determination of λ_z (and AUC_{0-inf}), the following conditions should be met:

- A minimum of at least 3 data points in the terminal elimination phase, in which C_{max} is not included;
- The Adjusted R-squared should be ≥ 0.8, and

- %AUCextrap < 20%.

If these conditions are not met, the PK parameter will be flagged in the listings (together with those dependent on λ_z, such as $t_{1/2}$, CL/F and V_z/F) and they may be excluded from the summary statistics. The decision to include these parameters will be based on the decision of the Sponsor with input from the pharmacokineticist.
The following flags/footnotes may be applied to the PK parameters:

Flag	Footnote
a	Adjusted R-squared of regression was <0.8
b	Extrapolated portion of $AUC_{0\text{-inf}}$ >20%
c	Insufficient post-C_{max} data points for estimation of lambda-z
d	Regression line could not be fitted

If plasma concentrations are all below the limit of quantification (BLQ), then PK parameter estimation and all subsequent statistical summaries will not be possible.

Whole blood to plasma concentration ratios will be determined on Day 1 at 1 hour, 2 hours and 6 hours.

4.13.1 Statistical Analysis on PK Parameters

PK analyses from blood samples will be performed on the PK set.

Plasma concentrations, including whole blood to plasma concentration ratios, will be listed and summarised by time point (N - the number of participants, n – the number of samples, n(LLOQ) - the number of samples <LLOQ, arithmetic mean, SD - standard deviation, CV - coefficient of variation, geometric mean, median, minimum, maximum). If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, minimum, and maximum will be presented as 1, and the geometric mean and geometric CV will be denoted as zero.

The PK parameters (Table 5) will be listed for each participant and summarized for each treatment group using descriptive statistics by treatment (N - the number of participants, arithmetic mean, SD - standard deviation, CV - coefficient of variation, geometric mean, median, minimum, maximum) except t_{max}. The t_{max} summary statistics will be provided as n, minimum, median, and maximum only. For the calculation of summary statistics of PK parameters, all not reported values (parameters which cannot be calculated) will be set to missing. PK parameters will be presented as given in the raw data. Descriptive statistics for PK parameters will be reported to 3 significant figures.

In addition, concentration figures over time will be presented by subject (combined in one figure by treatment) as mean (± SD) concentration, both on linear and logarithmic scale. Figures will be presented by treatment. BLQ values will be set to 0 on the linear scale, and LLOQ x 0.5 on the logarithmic scale.

4.13.2 Dose Linearity Analysis

Dose proportionality of noribogaine pharmacokinetics will be evaluated using a power model regression approach, as recommended by FDA and EMA guidelines. The following PK parameters will be assessed across different dose levels: C_{max}, AUC_{0-12}, AUC_{0-24}, and AUC_{0-inf}.

The log-log regression model will be applied using the following equation:

$$\log(\text{PK Parameter}) = \beta_0 + \beta_1 \log(\text{Dose}) + \epsilon$$

where β_1 (slope) represents the dose proportionality exponent. Dose proportionality will be concluded if β_1 lies within the acceptance range of 0.75–1.25 and its 90% confidence interval (CI) includes 1.

To further support the assessment, descriptive statistics for dose-normalized PK parameters (C_{max}/Dose and AUC/Dose) will be presented.

4.14 Methods for Withdrawals, Missing Data and Outliers

Unrecorded values will be treated as missing. The appropriateness of the method(s) for handling missing data may be reassessed at the data review prior to database lock where handling of outlier data and implausible data will also be discussed. Unscheduled measurements will be excluded from analysis and will be listed only. Data from subjects who withdraw early from the trial will be included in the analysis up to the point of their withdrawal. Missing data after withdrawal will not be imputed, and no additional assumptions will be made

5. REFERENCES

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5. Ferber G, Darpo B, Garnett C, Huang D, Marathe DD, Sun Y, Liu J. Detection and impact of hysteresis when evaluating a drug's QTc effect using concentration-QTc analysis. Journal of Pharmacokinetics and Pharmacodynamics. 2021;48(2):187-202. https://doi.org/10.1007/s10928-020-09725-w.

Appendix 1

ECG/PK allowable time windows - extracted from the data handling protocol.

Visit	Timepoint	ECG (min)	PK Plasma (min)	Combined (min)
D-1	H-0.5	±5		
D-1	H0	±5		
D-1	H1	±5		
D-1	H1.5	±5		
D-1	H2	±5		
D-1	H2.5	±5		
D-1	H3	±5		
D-1	H3.5	±5		
D-1	H4	±5		
D-1	H6	±5		
D-1	H7	±5		
D-1	H8	±5		
D-1	H11	±5		
D-1	H12	±5		
D-1	H12.5	±5		
D-1	H13	±5		
D-1	H13.5	±5		
D-1	H14	±5		
D-1	H14.5	±5		
D-1	H15	±5		
D-1	H16	±5		
D1	H-0.5(Pre-Dose)	±5		
D1	H0(Dose)	-15	-10	5
D1	H1	±5	±5	10
D1	H1.5	±5	±5	10
D1	H2	±5	±5	10
D1	H2.5	±5	±5	10
D1	H3	±5	±5	10
D1	H3.5	±5	±5	10
D1	H4	±5	±5	10
D1	H6	±5	±5	10
D1	H7	±5		
D1	H8	±5	±5	10
D1	H11	±5		
D1	H12(Dose)	-15	-10	5
D1	H12.5	±5		
D1	H13	±5	±5	10
D1	H13.5	±5	±5	10
D1	H14	±5	±5	10

Visit	Timepoint	ECG (min)	PK Plasma (min)	Combined (min)
D1	H14.5	±5	±5	10
D1	H15	±5	±5	10
D1	H16	±5	±5	10
D2	H0(Dose)	-15	-10	5
D2	H2	±5	±5	10
D2	H12(Dose)	-15	-10	5
D2	H14	±5	±5	10
D3	H0(Dose)	-15	-10	5
D3	H1	±5	±5	10
D3	H1.5	±5	±5	10
D3	H2	±5	±5	10
D3	H2.5	±5	±5	10
D3	H3	±5	±5	10
D3	H4	±5	±5	10
D3	H6	±5		
D3	H8	±5		
D3	H12(Dose)	-15	-10	5
D3	H14	±5	±5	10
D3	H15	±5		
D4	H0(Dose)	-15	-10	5
D4	H2	±5	±5	10
D4	H7	±5		
D4	H12(Dose)	-15	-10	5
D4	H14	±5	±5	10
D5	H0(Dose)	-15	-10	5
D5	H2	±5	±5	10
D5	H7	±5		
D5	H12(Dose)	-15	-10	5
D5	H14	±5	±5	10
D6	H0(Dose)	-15	-10	5
D6	H2	±5	±5	10
D6	H7	±5		
D6	H12(Dose)	-15	-10	5
D6	H14	±5	±5	10
D7	H0(Dose)	-15	-10	5
D7	H2	±5	±5	10
D7	H7	±5		
D7	H12(Dose)	-15	-10	5
D7	H14	±5	±5	10
D8	H-1(Pre-Dose)	±5		
D8	H0(Dose)	-15	-10	5

Visit	Timepoint	ECG (min)	PK Plasma (min)	Combined (min)
D8	H1	±5	±5	10
D8	H1.5	±5	±5	10
D8	H2	±5	±5	10
D8	H2.5	±5	±5	10
D8	H3	±5	±5	10
D8	H3.5	±5	±5	10
D8	H4	±5	±5	10
D8	H6	±5	±5	10
D8	H7	±5		
D8	H8	±5	±5	10
D8	H12	±5	±5	10
D8	H12.5	±5		
D8	H14	±5	±10	15
D8	H16	±5	±10	15
D9	H24	±10	±10	20
D9	H30	±10	±10	20
D9	H36	±10	±10	20
D10	H48	±10	±10	20
D10	H55	±10	±10	20
D10	H56	±10	±10	20
D11	H72	±10	±10	20

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