Statistical Analysis Plan

Study ID: 219882

Official Title of Study: An Open-Label, Single Arm, Dose Escalating Concentration-QT Study to Investigate the Cardiac Effects and Safety of Paroxetine in Healthy Adult Participants

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GSK 219882

An Open-Label, Single Arm, Dose Escalating Concentration-QT Study to Investigate the Cardiac Effects and Safety of Paroxetine in Healthy Adult Participants

Statistical Analysis Plan

Version: 1.0

Parexel Project Number: 275921

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Final 1.0	Date of Last Signature	Final document

LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition/Expansion
AE	Adverse event
BL	Biostatistician Lead
BLQ	Below the lower limit of quantification
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
C_{max}	Maximum observed concentration
CPMS	Clinical Pharmacology, Modeling, and Simulation
CRF	Case Report Form
CS	Clinically significant
CV	Coefficient of variation
DBP	Diastolic blood pressure
DRM	Data Review Meeting
ECG	Electrocardiogram
ENR	Enrolled Analysis Set
EOS	End of study
ET	Early termination
HR	Heart rate
IMP	Investigational medicinal product
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
PCS	Potentially clinically significant
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
QTc	corrected QT interval

Abbreviation/Acronym	Definition/Expansion
QTcF	QT corrected using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TEMA	Treatment-emergent markedly abnormal
WHO-DD	World Health Organization - Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of Study GSK 219882 (Parexel study number: 275921), An Open-Label, Single Arm, Dose Escalating Concentration-QT Study to Investigate the Cardiac Effects and Safety of Paroxetine in Healthy Adult Participants.

The content of this SAP is based on following study documents:

- Study GSK 219882 protocol Version 2.0 (15 Sep 2023).

This SAP will be finalized prior to database lock. Any changes after the finalization of this SAP will be documented in Statistical Method Modification Form.

2 STUDY OBJECTIVES

The objectives of the study are mentioned below:

2.1 Primary Objective

- To evaluate the potential effect of paroxetine on QTc interval following oral doses of 20, 40, and 60 mg once daily in healthy adults.

- **Primary Estimand:**
  The primary question of interest: Is there a clinically relevant cardiac effect of paroxetine at the maximum recommended therapeutic dose, as measured by an increase in QTc from 12-lead electrocardiogram (ECG)?

  The estimand is described by the following attributes:
  - Population: Healthy participants of age 18 to 65 years
  - Treatment condition: Dose up titration of paroxetine doses of 20, 40 and 60 mg
  - Endpoint: Change in QTc from baseline (ΔQTc)
  - Summary measure: The upper limit of the 90% confidence interval (CI) of model-predicted ΔQTc at the geometric mean steady-state Cmax of the 60 mg paroxetine dose
  - Intercurrent events:
  - a) Treatment discontinuation due to any reason - While on-treatment strategy will be applied to address this intercurrent event.
  - b) Any events affect the drug absorption (1 hour) – Treatment Policy strategy will be applied to address this intercurrent event.
- **Rationale for Estimand:**
  a) Interest lies in establishing the relationship between ΔQTc and paroxetine concentrations while the participant is exposed to paroxetine as planned, i.e., prior to the discontinuation of the treatment.
  b) Interest lies in the overall relationship between the ΔQTc and paroxetine concentrations, not with dose - therefore even though the concentration for a dose is affected, the data are still relevant even when there is an inaccuracy in dosing.

If this summary measure is ≥10 msec, additional summary measure may be generated at the geometric mean C_{max} of the 40 mg dose. Additionally, another estimand might need to be evaluated.

2.2 Secondary Objective

- To assess the safety and tolerability of paroxetine doses of 20, 40, and 60 mg once daily in healthy adults.

- **Secondary Estimand:**

Secondary estimand address all other safety and tolerability findings.

The estimand is described by the following attributes:

- Population: Healthy participants of age 18 to 65 years
- Treatment condition: Dose up and down titration of paroxetine doses of 20, 40 and 60 mg
- Endpoint:
  - Occurrence of adverse events (AEs) and serious adverse events (SAEs)
  - Changes in vital signs (blood pressure, heart rate and oral body temperature) from baseline
  - Changes in hematological and clinical laboratory tests from baseline
- Summary measure: Proportions for AEs and SAEs and means of the change from baselines for vital signs, hematological, and clinical laboratory across all dose levels.
- Intercurrent events: Study intervention discontinuation due to any reason – treatment policy strategy will be applied for this intercurrent event.
- Rationale for Estimand: Safety data will be monitored throughout the study after the start of study intervention. There is interest in evaluating and reporting safety events regardless of whether participants discontinued study intervention.

2.3 Exploratory Objective(s)

Not Applicable

3 INVESTIGATIONAL PLAN

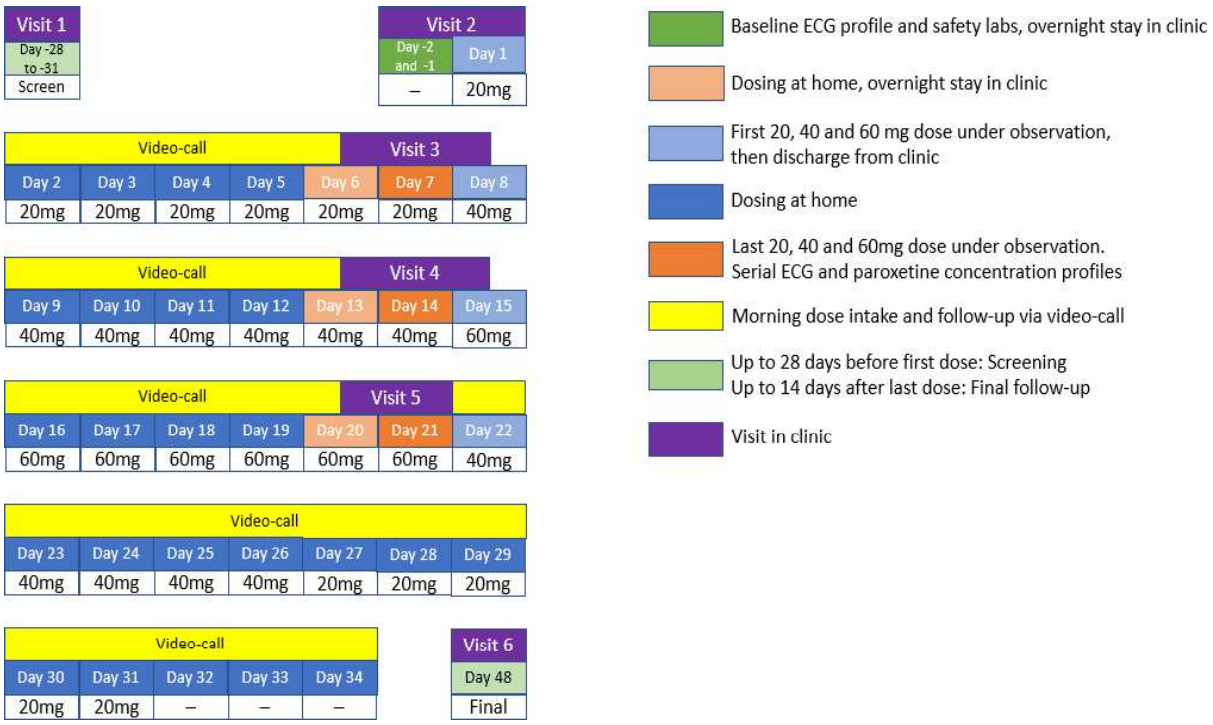
3.1 Overall Study Design and Plan

This is a an open-label, single arm, dose-escalating concentration QT study to investigate the cardiac effects, safety and tolerability of paroxetine in healthy adult participants.
At least 36 participants with no history of cardiac abnormalities or mood disorders will be enrolled. All eligible participants will receive paroxetine titrated to a dose of 60 mg once daily at increments of 20 mg per week.
All participants will attend a study site visit at Screening (Visit 1: -28 to -31 days), baseline (pre-dose) assessments and first paroxetine administration of 20 mg once daily (Visit 2: Day 1), serial ECG and paroxetine concentration measurements (Visit 3, Day 7) and dose escalation to 40 mg once daily (Visit 3: Day 8), serial ECG and paroxetine concentration measurements at the 40 mg dose (Visit 4, Day 14) and dose escalation to 60 mg once daily (Visit 4: Day 15), serial ECG and paroxetine concentration measurements (Visit 5, Day 21) and the Exit visit (Visit 6, up to 14 days after last 20 mg dose). Tapering from 60 to 40 mg once daily, 40 to 20 mg once daily, and 20 mg once daily to no dose will occur at home. Unplanned visits (if needed) will be scheduled for participants who needs to visit the clinic due to AEs during home dosing or required to start intermediate tapering dose of 10 mg to be started (for both clinic and home dosing) during the tapering period.

During home dosing participants will be interviewed remotely via video-call to confirm dosing compliance and have daily follow-ups.

The study design schema is presented in Figure 1-1

Figure 1-1Study Design Overview



3.2 Endpoints and Associated Variables

The following list of study endpoints and associated variables will be used to Investigate the Cardiac Effects and Safety of Paroxetine in Healthy Adult Participants.

3.2.1 Primary Endpoint

- Change in QTc from baseline (ΔQTc)

3.2.2 Secondary Endpoint

- Changes in vital signs (blood pressure, heart rate and oral body temperature) from baseline

- Occurrence of adverse events (AEs), serious adverse events (SAEs), hematological and clinical laboratory tests, vital signs, and physical examination

3.2.3 Pharmacokinetic Variables

Pharmacokinetic concentration data will be obtained at time point(s) described in the schedule of assessment in Section 6.1.

Unless otherwise stated, derivation of PK parameters will be the responsibility of CPMS group, Parexel.

The following plasma PK parameters listed in Table 3-1 for paroxetine following repeated dose administration will be determined using non-compartmental analysis.

Table 3-1Plasma Pharmacokinetic Parameters after Multiple Dose Administration after Last Dose (on Day 7, 14 and 21)

Parameter	WNL Name	CDISC Name	Definition
C_{max}	Cmax	CMAX	Maximum observed concentration in a dosing interval after last dose administration
t_{max}	Tmax	TMAX	Time corresponding to occurrence of C_{max} after last dose administration

3.2.4 Safety Variables

- Physical examinations
- Vital signs (Blood Pressure, heart rate and oral body temperature)
- 12-lead electrocardiogram (ECG): Heart rate, PR interval, Q waves, QRS interval, QTcF interval
- Clinical laboratory tests (haematology, clinical chemistry, coagulation, and pregnancy testing, other screening tests.)
- Adverse event (AE)/serious adverse event (SAE) assessments
- Prior and concomitant medication assessments
- Pregnancy test

3.2.5 Exploratory Variables

Not Applicable.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity, and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

This section is not applicable to PK data.

4.2.1 Treatment

All participants will receive active treatment with paroxetine tablets once daily with titration steps every week over a maximum treatment period of 3 weeks. This is followed by tapering over the subsequent period of 10 days:

- Days 1-7: 20 mg once daily
- Days 8-14: 40 mg once daily
- Days 15-21: 60 mg once daily
- Days 22-26: 40 mg once daily
- Days 27-31: 20 mg once daily. If participants are not able to withdraw from 20 mg once daily directly due to withdrawal effects, an additional tapering dose step of 10 mg once daily may be given for 5 days. Unplanned visits (if needed) will be scheduled for participants who need to visit to clinic due to AEs during home dosing or required to start intermediate tapering dose of 10 mg to be started (for both clinic and home dosing) during the tapering period.
- Day 32 (or 37) onwards: complete stop of paroxetine

4.2.2 Study Day

Study days will be numbered relative to the first day of study drug administration.

- If the date of event is before the study drug administration, then:

  Study day = (Date of event – Date of study drug administration [i.e. Day 1])

- If the date of event is on or after the study drug administration, then:

  Study day = (Date of event – Date of study drug administration [i.e., Day 1]) + 1

- If the date of event is missing, then study day is also missing.

4.2.3 End of Study

A participant is considered to have completed the study if they have completed all phases of the study. including the last visit for any protocol-related activity (last participant, last visit) as shown in the SoA (Section 6.1) are completed.

The end of the study is defined as the last visit of the last participants in the study.

4.2.4 Baseline

Baseline is defined as the mean of Day -1 timepoints recorded before first dose of study treatment administration for all types of measurements except for primary analysis.

The baseline definition will be used for following safety variable:

- Vital signs
- Clinical laboratory tests

4.2.5 Controlled, Repeat, Retest, Scheduled and Unscheduled Assessment

Repeat, retest, and unscheduled assessment will not be considered for the calculation of summary statistics and figures, unless assessment qualifies as baseline.

Average of controlled and planned (scheduled) assessment will be considered for the calculation of summary statistics and figures, if more than one controlled/planned assessment will be performed at a specific time point.

4.2.6 Summary and Representation of Data

Continuous data will be summarized in terms of mean, standard deviation (SD), median, minimum, maximum, and number of observations, unless otherwise stated.

Categorical data will be summarized in terms of the number of participants providing data at the relevant time point (n), frequency counts, and percentages.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistics.

Percentages between 1% and 99%, inclusive, will be rounded to integers. Percentages greater than 0%, but less than 1%, will be reported as <1%, and percentages greater than 99%, but less than 100%, will be reported as >99%. If for any summary table, n is less than three then only n, minimum, and maximum should be presented, and other summary statistics will be left blank.

4.3 Software

All report outputs will be produced using SAS® version 9.3 or later in a secure and validated environment.

The PK analyses will be conducted using Phoenix® WinNonlin (WNL) version 8.3 or later in a secure and validated environment.

All report outputs will be provided to the Sponsor in RTF for individual TLFs and PDF for combined TLFs format.

4.4 Study Participants

4.4.1 Analysis Sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Enrolled	• All participants who entered the study (who successfully passed screening) • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	• Study Population
Safety/Exposed	• All participants who received at least one dose of study intervention.	• Safety

Analysis Set	Definition / Criteria	Analyses Evaluated
	• Data will be reported according to the actual study intervention.	
PK	• All participants in the Safety analysis set who had at least 1 non-missing PK assessment (non-quantifiable values will be considered as non-missing values). • Data will be reported according to the actual study intervention. • Used for some displays required by EudraCT. Studies with single arm should use the text "Assigned rather than Randomized".	• Primary analysis
PD	• All participants in the Safety analysis set who had at least 1 non-missing ECG assessment. • Data will be reported according to the actual study intervention.	• Primary analysis

4.4.2 Disposition of Participants

A clear accounting of the disposition of all participants who enter the study will be provided, from screening to study completion.

A summary of participant study/treatment completion status and reason for study withdrawal will be provided for the enrolled set. This display will show the number and percentage of participants who withdrew from the study, who have completed the study or have discontinued study treatment including primary reasons for study withdrawal and discontinuation of study treatment.

A by participant listing of study discontinuation will be presented for the enrolled set. The listing will include last dose date and reasons for study treatment discontinuation.

A by participant listing for screen failure will be provided including reason for screen failure for all participants.

4.4.3 Protocol Deviations

All protocol deviations are predefined in the separate document, Protocol Deviation Assessment Plan.

4.4.3.1 Protocol Deviations with Non-PK Implications

The defined protocol deviations will be collected during the study period by site monitor/clinical team and programming team. All deviations will be described when relating to:

- Study inclusion or exclusion criteria
- Conduct of the study
- Participant management or participant assessment
- Handling of the participant's rights.

4.4.3.2 Protocol Deviations with PK Implications

Protocol deviations that may potentially impact PK parameter derivations include, but are not limited

to:

- Emetic episode within 1 hour afteradministering study drug
- Missed PK samples that impact estimation of PK parameter(s)
- Concomitant medications not authorized by protocol.
- PK samples obtained out of allowance window that may impact the estimation of PK parameter(s)
- Food intake deviations (not completely consumed or consumed outside of time allowed)

Protocol deviations (mentioned in Sections 4.4.3.1 and 4.4.3.2) and analysis sets will be reviewed in the (blinded) data review report meeting to decide inclusion or exclusion of participant(s) from analyses sets. Decisions regarding the exclusion of participants and/or participant data from analyses will be made prior to database lock and will be documented and approved.

A by-participant listing of important and non-important protocol deviations will be provided including participant identifier; exclusion from specific analysis sets; and protocol deviation classification, and protocol deviation description and exclusion from specific analysis sets.

4.5 Demographics and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, height, body weight, body mass index [BMI]) will be summarized and listed by participant for the Safety Set and enrolled set.

Age, height, weight and BMI will be summarized using the mean, SD, minimum, median, and maximum. The count and percentage will be computed for sex, race, and ethnicity. The summary table will be displayed by treatment for the Safety Set.

4.6 Medical History

Medical and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA®), Version 26.0 or higher and assigned to a System Organ Class (SOC) and Preferred Term (PT). Summary of Medical history will be provided by SOC and PT for Safety Analysis Set.

4.7 Prior and Concomitant Medications

Prior and Concomitant Medication:

Prior medications are those that started and stopped before the first dose of IMP. Concomitant medications are those taken after first dosing (including medications that started before dosing and continued after).
Prior and concomitant medication will be coded according to the World Health Organization Drug Dictionary (WHO-DD) (Version March 1, 2023 or latest) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.
By participant listings of prior and concomitant medications will be provided for the Safety Set and will include the following information: reported name, preferred term (PT), the route of administration, dose, frequency, start date/time, duration, and indication.

4.8 Treatment Exposure and Compliance

4.8.1 Treatment Exposure

Summary of treatment exposure will be provided in terms of number of dose administered based on Safety population for the IP administration. A by-participant listing of participant exposure to study

drug will be generated. The listing will include dose, date and time, unit, formulation, route, and frequency.

4.8.2 Compliance

Dose compliance at site and dosing compliance while dosing at home will be evaluated. Participants will take the planned dose under direct supervision while on site, and via video-call while dosing at home.

- Compliance (%) at site will be calculated as 100% * total number of actual taken site doses / total number of planned site doses.
- Compliance (%) at home will be calculated as 100% * total number of actual taken home doses/ total number of planned home doses.

4.9 Analysis Supporting Primary Objective(s)

4.9.1 Primary Endpoint(s)

The primary endpoint is the change from baseline in QTc (ΔQTc), where baseline is the pre-dose collection obtained on visit 2 (Day -1, 0.25h before the planned dosing time of Day 1).

QTc for primary analysis will be measured at Visits 2 (Day -1), 3 (Day 7), 4 (Day 14) and 5 (Day 21) as outlined in the SoA. At each time point where replicate ECG is obtained, then mean of the triplicates will be used for deriving baseline and change from baseline.

4.9.2 Statistical Hypothesis, Model, and Method of Analysis

A random-coefficient linear mixed-effects model will be fit to all available paroxetine concentration - ΔQTc data pairs, as described in a white paper (Garnet C et al., 2018 [3]). In this model, ΔQTc is the dependent variable and paroxetine concentration and time after dose and baseline are independent variables, it takes the form of:

$$\Delta QTc_{i,k} = (\theta_0 + \eta_{0,i}) + (\theta_1 + \eta_{1,i}) * C_{i,k} + \theta_{2,k} * TIME_{i,k} + \theta_3(QTc_{i,k=0} - \overline{QTc_0}) + \varepsilon_{i,k}$$

In this equation:

- $\Delta QTc_{i,k}$ is the change from baseline in QTc for participant i at time k;
- θ_0 is the population mean intercept in the absence of a treatment effect;
- $\eta_{0,i}$ is the random effect associated with the intercept term θ_0;
- θ_1 is the population mean slope of the assumed linear association between concentration and $\Delta QTc_{i,k}$;
- $\eta_{1,i}$ is the random effect associated with the slope θ_1;
- $C_{i,k}$ is the concentration for participant i and time k;
- $\theta_{2,k}$ is the fixed multilevel categorical effect associated with time factor. If inspection of the Day -1 data suggests a time-dependent trend, alternative parameterization for the time variable, for example based on (co)sine function such as described in Koch et al 2002, could be used if relevant;
- θ_3 is the fixed effect associated with the difference of each baseline values to the overall mean (Baseline $QTc_{i,k=0}$, QTc_0 is overall mean of $QTc_{i,k=0}$, i.e., the mean of all the baseline (= time 0) QTc values).

It is assumed the random effects ($\eta_{0,I}$ and $\eta_{1,i}$) are normally distributed with mean [0,0] and an unstructured covariance matrix G, whereas the residuals are normally distributed with mean 0 and variance R. In case of the unstructured covariance matrix for random effects is not supported by the data or results in null estimates, and may result in non-convergence problems, other simplified or reduced structures will be investigated (Variance component with 2 random effects,1 for slope and 1 for intercept, variance component with 1 random effect for intercept or slope).

The ΔQTc and paroxetine concentrations corresponding to all doses (20, 40, and 60mg) will be used for the modelling (Both drawn from each participant at same time intervals). Moreover, ΔQTc obtained on Visit 2 (Day -1) after baseline will be included in the model with paroxetine concentrations set to 0. This model assumes a linear correlation between paroxetine plasma concentration and ΔQTc. While it is assumed that such a correlation (if at all) can be considered linear at clinically meaningful doses, other parameterizations such as the classical Emax function may be explored if the linear approach is found inappropriate.

The model parameters will be estimated including the precision around the parameter estimates using a maximum likelihood approach.

The following SAS® code will be used for the random-coefficient linear mixed-effects model:

```
PROC MIXED DATA=ADEG(WHERE=(XXXX)) NOITPRINT CL NOCLPRINT  METHOD=ML PLOTS=NONE;

ODS OUTPUT SOLUTIONF=SOLF ESTIMATES=ESTF COVPARMS=COV;

CLASS USUBJID ATPTN ;

MODEL CHG=BASEC ATPTN PCSTRESN / DDFM=KR SOLUTION ALPHAP=.05 CL RESIDUAL
OUTPM=PRED OUTP=IPRED;

RANDOM INT PCSTRESN /SUB=USUBJID TYPE=UN;

ESTIMATE "DDQTC_60MG" INT 1  PCSTRESN CMAX60MG /CL ALPHA=.1;

RUN;
```

4.9.2.1 Underlying assumptions

Effect on HR

Time course of mean changes in HR will be displayed by dose as detailed in Section 4.12.5.

Appropriateness of the QT correction off-drug (QTc is independent of HR):

In healthy participants, Fridericia correction of the QT interval (QTcF) is usually considered appropriate for drugs with limited effects on HR. QTcF is computed as QTcF (msec) = $QT/(RR/1000)^{1/3}$.

The appropriateness of the correction can be assessed by determining if the QTc is independent of the HR using drug free data. For that purpose, a scatter plot of QTcF values (y-axis) versus HR values (x-axis) obtained at Visit 2 (Day -1) will be provided with linear and non-linear (loess) regression lines to assess the lack of relationship between QTcF and HR off-drug. Moreover, similarity of the range of HR off- and on-drug, to support the correction in both cases, will be assessed by plotting the mean QTcF values calculated by decile of HR for each visit (off-drug on Visit 2 and on-drug on Visit 3, 4 and 5). Linear mixed effects lines and 95% confidence intervals computed for each visit will be plotted on the same graph.

Appropriateness of the QT correction on-drug:

In addition, the potential of paroxetine to significantly increase of decrease HR should be evaluated. Mean increase or decrease > 10 beats/min are considered sufficient to impact the quality of the Fridericia correction and the primary endpoint assessment. The impact of paroxetine on HR will be

assessed from the graphical display of change from baseline in HR (ΔHR) described in Safety Evaluation (Section 4.12.5).
If these graphical explorations suggest insufficient HR correction of the QT interval, alternative corrections, such as Bazett (QTcB (msec) = QT/(RR/1000)$^{1/2}$), could be evaluated.

No time delay between drug concentration and effect on QTc (direct effect hypothesis, no PK/PD hysteresis):
The direct temporal relationship between paroxetine concentrations and ΔQTcF will be assessed graphically by plotting the time course of mean ΔQTcF with the time course of paroxetine concentrations geometric mean by visit. If for the two highest doses of paroxetine (Visits 4 and 5) a delay (hysteresis) between the time to reach the peak concentration and the peak QTc effect is more than 1 hour, other modeling strategy may be explored.

Linear relationship between paroxetine relationship and ΔQTcF
The linear relationship will be assessed using a scatter plot of ΔQTcF (y-axis) vs. concentrations (x-axis), with linear and non-linear (loess) trend lines. The trend lines, directly obtained from the SAS® graphical procedures, will not reflect the model fit of the data but rather rough fixed regressions (without random effects) to detect drug effect and whether there are major violations to the linear assumption (in case of drug effect)
In case of the linearity assumption cannot be accepted, alternative models will be explored. A non-linear alternative could be, for example, the Emax model for which the linear component $((\theta_1 + \eta_{1,i}) * C_{i,k})$ is replaced by a component of the form $(\theta_{1,1} + \eta_{1,i}) * C_{ik}^{\gamma}/(\theta_{1,2}^{\gamma} + C_{ijk}^{\gamma})$, where $\theta_{1,1}$ is the maximal asymptotic increase from θ_0 , $\theta_{1,2}$ is the concentration at which the effect is half $\theta_{1,1}$, γ is the hill coefficient and $\eta_{1,i}$ is the random effect associated with $\theta_{1,1}$.
As such an example for a full nonlinear model could be written as :

$$\Delta QTc_{i,k} = (\theta_0 + \eta_{0,i}) + (\theta_{1,1} + \eta_{1,i}) * \frac{C_{ik}^{\gamma}}{\theta_{1,2}^{\gamma} + C_{ik}^{\gamma}} + \theta_{2,k} * TIME_{i,k} + \theta_3(QTc_{i,k=0} - \overline{QTc_0}) + \varepsilon_{i,k}$$

The model parameters will be estimated including the precision around the parameter estimates using a maximum likelihood approach. Initial values will be determined from the graphical display.

Categorical description of time effect on ΔQTcF
The standard model contains a categorical variable to account for time dependent changes in QTc ($\theta_{2,k} * TIME_{i,k}$). This parameterization is agnostic to any trends in such changes, and may be better represented by other functions. In particular, it has been reported in literature that (co)sinusoidal functions may describe the change in QTc due to diurnal / circadian variation, e.g. Koch & Raschka 2002 [5]. Inspection of the Day -1 serial QTc data may help to elucidate such trends in change of QTc over time and drive the specification of such a time-dependent function.

4.9.2.2 Model evaluation

Diagnostic and goodness of fit plots will be presented for the final model and will include:
- Quantile-Quantile plots of residuals;
- Concentrations versus residuals;
- Time and baseline versus residuals;
- Model predicted ΔQTc versus observed ΔQTc plotted with a loess line.
- Mean observed and predicted ΔQTc by deciles of concentrations (quantile plot) with model slope and 90% CI.

4.9.2.3 Summary of measure

Individual Cmax values for participants at the 60 mg dose will be used to calculate the Cmax geometric mean. Based on the estimated model, the calculated geometric mean Cmax for dose 60 mg will be used in the fitted model to predict the upper limit of the 90% CI of ΔQTc at dose 60 mg as follows (in the case of a linear model):

$$\overline{\Delta QTc_{60mg}} = \theta_0 + \theta_1 Cmax(60mg)$$

$$90\%\ CI\ =\ \overline{\Delta QTc_{60mg}}\ \pm\ t(0.95, DF)\ \text{x SE}$$

$$SE = \sqrt{var(\theta_0) + C_{max}^2(60\ mg)var(\theta_1) + 2C_{max}(60\ mg)\ \times cov(\theta_0, \theta_1)}$$

Where:

- $\overline{\Delta QTc_{60mg}}$ is the predicted ΔQTc at 60 mg;
- θ_0 is the estimated fixed intercept term;
- θ_1 is the estimated fixed slope for concentrations;
- $t(0.95,DF)$ is the 95th quantile from the student distribution with DF degrees of freedom;
- SE is the standard error ;
- var(θ_0), var(θ_1) and cov(θ_0,θ_1) are respectively the variance of θ_0 and θ_1 and their covariance.

The summary measure of the study is the geometric mean and 90% CI of the predicted ΔQTc at 60 mg Cmax. If the upper bound of 90% CI for this predicted ΔQTc falls below the 10 msec mark, the conclusion of the study is that there is no clinically relevant QTc prolongation up to and including the 60 mg dose. In case the upper 90% CI limit does not fall below the 10 msec mark, the same evaluation will be performed for the ΔQTc at the geometric mean Cmax of the 40 mg once daily dose.

4.9.3 Handling of Intercurrent Events

The following intercurrent event will be considered:

a. Treatment discontinuation due to any reason - While on-treatment strategy will be applied to address this intercurrent event.
   The data affected by occurrence of the intercurrent event would be treated as missing at random from the occurrence of the intercurrent event until the end of the study. Participant level missing data considered as missing at random, will not be imputed and available data will be used in the primary analysis.

b. Any events affect the drug absorption (1 hour) – Treatment Policy strategy will be applied to address this intercurrent event for the estimation model as it is based on concentration not dose - therefore even though the concentration may be affected, the data is still relevant for quantifying the relationship between change in QTc and drug concentration. Hence, we will use all the data in the modelling (paroxetine concentration and ΔQTc) irrespective of the occurrence of the intercurrent event. However, when the model is used to predict the upper 90% CI for 60mg doses an absorption event may artificially reduce the prediction, hence the corresponding paroxetine concentration data will not be used in the calculation of the Cmax at and in the prediction of the geometric mean of predicted ΔQTc and 90% CI.

4.9.4 Handling of Missing Values not Related to Intercurrent Event

Missing data not related to intercurrent event will not be imputed and available data will be used in the primary analysis.

4.9.5 Sensitivity analyses

A sensitivity analysis will be performed to ensure that there is no bias in the calculated geometric mean of the Cmax at the 60 mg once daily dose, in case:

- Twenty percent (20%) or more of the total PK data is missing, or
- Twenty percent (20%) or more of participants (8 participants or more) at the 60 mg once daily dose have either missing paroxetine concentration data around the Cmax at the 60 mg dose level, or an intercurrent event of "any events affecting absorption within 1 hour of the dose" at the 60 mg dose

This analysis will consist of a population pharmacokinetic (PopPK) model-fitting of the individual paroxetine concentration data without the estimation of population level parameters (post-hoc or Bayesian fit), using a paroxetine popPK model developed internally at GSK. Appropriateness of the available paroxetine popPK model will be determined based on goodness-of-fit plots (e.g. population and individual prediction [PRED, IPRED] vs observed concentrations [DV], CWRES vs IPRED). A descriptionof the popPK model, if used for sensitivity analysis, will be included in the study report.

The individual PK parameters from the Bayesian model fit will allow the model-based individualised prediction of the Cmax at the 60 mg once daily dose for those participants with missing data, based on the available paroxetine concentration data at the earlier doses. Through this method, a geometric mean of Cmax at the 60 mg dose can be calculated that should be less affected by dropout, missing data, or intercurrent events. An additional calculation of the upper limit of the 90% CI of ΔQTc will then be performed using the Cmax of the 60 mg dose calculated using this method. In case the evaluation of ΔQTc finds a ≥10 ms upper 90% CI limit at the 60 mg dose, the same model-based prediction of Cmax at the 40 mg dose for dropouts will be performed, where required. If such a sensitivity analysis is performed, results from both the regular analysis (without PK model fitting and predictions) and the sensitivity analysis will be presented in the study report.

4.9.6 Supplementary analyses

Not applicable.

4.10 Analysis Supporting Secondary Objective(s)

Analysis Supporting secondary Objective are described in section 4.12.

4.11 Pharmacokinetic Analysis, Concentration, and Parameter TFLs, and Statistical Analysis of Pharmacokinetic Parameters for Final Analysis

4.11.1 Pharmacokinetic Concentrations

Concentration Listings:

Pharmacokinetic concentration data for paroxetine will be listed by participant for the Safety analysis set. Concentration listings will include nominal PK sampling time, actual sampling times relative to dose administration, deviation from nominal time, and percent deviation from nominal time, and concentrations. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as below the lower limit of quantification (BLQ) in the listings and the LLOQ value presented as a footnote. Missing PK samples will be reported in the (blinded) data review meeting report (see section 4.4.3) and not reportable samples will be reported as NR, in listings and considered excluded from PK analysis.

Concentration Summary Tables:

Source data as reported from the laboratory will be used for calculation of concentration summary statistics. Tabular summaries for concentration-time data will report N (number of subjects included in the PK population for each dose), n (number of subjects at a given timepoint), and n(BLQ) (the number of subjects with BLQ samples).

Concentration for paroxetine will be summarized by dose, and nominal timepoint for the PKAS. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: N, n, n(BLQ), arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV% =SQRT(e^{s^2}-1)*100; where s is the SD of the log-transformed values), 95% CI, median, minimum, and maximum values.

For summary tables, all BLQs will be replaced with zero except when an individual BLQ falls between two quantifiable values, in which case it will be omitted for the calculation of all summary statistics. For the calculation geometric mean and geometric CV%, BLQ values will be replaced by half the LLOQ value instead of zero. Summary statistics will not be calculated if non-BLQ concentrations at a scheduled time point is <3 and will be reported as NC, with the exception of minimum and maximum; minimum will be reported as "BLQ" and in case of all BLQ values, also maximum will be reported as "BLQ".

The rules followed for calculation and presentation of concentration data with regards to the number of decimal places/significant digits for the listings of participant level concentrations and summary tables of concentration are as follows:

Concentration Listings and Tables	Rounding
Individual concentrations	*n* s.f. as supplied by bioanalytical laboratory
Minimum and Maximum	*n* s.f. as original data
Mean/Median/Geomean	*3* s.f.
SD, CI	*4* s.f.
CV%/gCV%	*1* d.p.
N/n	Whole number

s.f = significant figures, d.p. = decimal place

Concentration Figures:

For arithmetic or geometric mean linear/linear graphs, the data plotted in the figure should match the data presented in the summary table, with the exception of values reported in table as NC prior to C_{max} which should be set to 0 in the figure (to capture lag-time). For arithmetic or geometric mean log/linear graphs, all values reported in table as NC will be set to missing.

For individual linear/linear and log/linear graphs all BLQ values will be substituted as follows:

- One or more BLQs at the beginning of a participant profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero. When using semilog scale, these timepoints will be considered missing.
- BLQs at the end of a participant profile (i.e., after the last incidence of a measurable concentration) will be set to missing.

- Single BLQs which fall between two measurable concentrations will be set to missing.
- More than one consecutive BLQs which fall between measurable concentrations will be set to zero, and the subsequent measurable concentrations will be retained.

To visualize participant-level concentrations and the comparison between groups for each dose, the descriptive PK graphs listed below will be generated. Include LLOQ line in individual and summary plots.

- Individual participant profiles for paroxetine plasma concentration time data – (linear scale and semi-logarithmic scale) (SAF)
- Overlaid individual participant profiles for paroxetine Plasma Concentration Time Data – (linear scale and semi-logarithmic scale) (SAF)
- Mean (± SD) paroxetine plasma concentration time data – (linear scale and semi-logarithmic scale) (PKAS)
- Median (range) paroxetine plasma concentration time data – (linear scale and semi-logarithmic scale) (PKAS)

Figures will be generated in black and white using unique line style and marker for each plot in the graph. For all PK concentration-time plots, a linear scale will be used for the x-axis (e.g., not an ordinal scale).

4.11.2 Pharmacokinetic Parameters

PK parameters will be provided by Parexel CPMS group. PK parameters will be calculated by NCA methods from the concentration-time data using Phoenix® WinNonlin® Version 8.3 or higher following these guidelines:

- Actual time from dose will be used in the calculation of all derived PK parameters, except when parameters are calculated for safety/dose escalation meetings when nominal times may be used to calculate PK parameters.
- Handling of BLQ samples for derivation of plasma PK parameters after each dose administration
    - BLQs at the beginning of a participant profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero.
    - BLQs at the end of a participant profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
    - Single BLQs which fall between two measurable concentrations will be set to missing.
    - Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will also be set to missing.

Pharmacokinetic parameters will be estimated according to the guidelines presented in Table 4-1.

Table 4-1 Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation
C_{max}, t_{max}	Obtained directly from the observed concentration-time data, unless specified otherwise (see Section 4.9.1).

PK Parameters Listings:

PK parameters will be listed by participant for the SAF. PK parameters that will be flagged and/or excluded from summary tables and statistical analyses of PK parameters will be flagged and footnoted with the reason for flagging/exclusion.

PK Parameter Summary Tables:

Biostatistics group will consider the derived PK parameters as source data and will use this data without rounding for calculation of PK parameters summary statistics tables.

PK parameters will be summarized by treatment for the PK Set.

Tabular summaries for PK parameters will report N (number of subjects included in the PK population for each dose) and n (number of subjects with a specific parameter).

Descriptive statistics for calculated PK parameters will include N, n, arithmetic mean, SD, CV%, geometric mean, gCV%, 95% CI, median, minimum, and maximum values. For t_{max}, only N, n, median, minimum, and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

The rules followed for presentation of PK parameters data with regards to the number of decimal places/significant digits for the listings of participant level PK parameters and summary tables of PK parameters are as follows:

PK Parameter Listings and Tables	Rounding
Derived Individual parameters	3 s.f.
Directly Derived Individual parameters (C_{max},)	*n* s.f. as supplied by the analytical laboratory but not more than 3 s.f.
Minimum and Maximum	3 s.f.
Mean/Median/Geomean	4 s.f.
SD	*5* s.f.
CV%/gCV%	1 d.p.
Comparative estimates (e.g. ratios)	3 d.p.
CI and other percentages	*4* s.f.
p-values	4 d.p.
N/n	Whole number
Exceptions for PK Tables	
t_{max} individuals and min/max	2 d.p
t_{max} median only	2 d.p

s.f = significant figures, d.p. = decimal place

4.12 Safety Evaluation

Secondary estimands address all other safety and tolerability findings.
Treatment policy strategy will be applied for Study treatment discontinuation due to any reason intercurrent event - Safety data will be monitored throughout the study after the start of treatment. There is interest in evaluating and reporting safety events regardless of whether participants discontinued treatment.

All safety analysis will be performed on the Safety Set. All participants who received treatment of study medication will be included in the safety analysis. Categorical data will be summarized using counts and percentages, however continuous data will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum for continuous data by dose.

4.12.1 Adverse Events

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.
All outputs for Adverse Events (AEs) will be based on the Safety Set unless specified separately in TLF shells.

Summaries of AEs will include the following:

- Incidence of AEs - Overview by dose and overall
- Incidence of AEs by dose, SOC, and PT
- Incidence of AEs by maximum causality, dose, SOC, and PT)
- Incidence of AEs by maximum intensity by dose, SOC, and PT)
- Adverse Events (AEs) Leading to discontinuation of study intervention by dose, SOC and PT
- Incidence of SAEs - Overview by dose and overall
- Incidence of SAEs by dose, SOC, and PT
- Summary of common (>=5%) non-serious adverse events (not included in the serious of adverse event) - Number of subjects and occurrences by SOC & PT
- Summary of drug related any adverse events – Number and percentage of subjects by SOC & PT
- Summary of fatal adverse events – Number and percentage of subjects by SOC & PT
- Summary of drug related fatal adverse events – Number and percentage of subjects by SOC & PT
- Summary of drug related non-serious adverse events - Number and percentage of subjects by SOC & PT

All TEAE summaries should provide the number and percentages of subjects reporting at least one TEAE and the total number of events reported.

Summaries of TEAEs will include the following:

- Incidence of TEAEs - Overview by dose and overall
- Incidence of TEAEs by dose, SOC, and PT

Summary tables will contain counts of participants, percentages of participants in parentheses, and the number of events where applicable. A participant who has multiple events in the same SOC and PT will be counted only once in the participant counts, but all events will be included.

A listing will be created for all Adverse Events (AEs), which will include study day, preferred term (PT), system organ class (SOC), AE onset date (and time), AE end date (and time) or ongoing,

duration of the AE, causal relationship to IMP, AE outcome, intensity and seriousness, action taken with IMP, concomitant medication (if administered), and TEAE indicator flag.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, and then alphabetically for SOC, and PT within SOC.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA®), Version 26.0 or higher).

All Adverse Events (AEs)

Treatment-emergent Adverse Event
A TEAE is defined as an AE that began after the start of trial medication treatment or if the event was continuous from baseline and was serious, trial medication-related, or resulted in death, discontinuation, or interruption or reduction of trial therapy, those TEAEs will be analysed for the purpose of safety analysis.

4.12.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

The following summary tables will be provided.

- Summary of all-cause mortality - Number of subjects and occurrences by SOC & PT
- Summary of serious adverse events - Number of subjects and occurrences by SOC & PT

The following listings will be provided.

- A by participant listing of all deaths that occurred during the study
- A by participant listing of all SAEs
- A by participant listing of all TEAEs leading to discontinuation of study treatment

4.12.3 Clinical Laboratory Evaluation

Clinical laboratory test results of haematology, clinical chemistry, coagulation, pregnancy testing and other screening tests (FSH and oestradiol as needed in WONCBP only, urine alcohol and drug screen, serology) will be provided by subject. A list of current reference ranges of laboratory assessments is included in Section 6.3. Since laboratory ranges can be subject to changes over time the reference ranges presented in Section 6.3 might differ from the ones used and presented on SDTM. For analysis purposes only the ranges present on the SDTM will be used.

All TLFs will display only the standard international (SI) units after conversion by means of standard conversion factors.

Quantitative clinical laboratory variables, ie, haematology, clinical chemistry, and coagulation will be summarized using descriptive statistics (n, mean, SD, minimum, maximum and median) by on/off treatment. Additionally, a within-participant change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way.

Baseline definition will be defined in section 4.2.4.

Each laboratory result will be classified as low (L), normal (N), or high (H) at each time point according to the laboratory supplied reference ranges. Tabulations will be presented by treatment (on/off treatment).

Measurements obtained at Screening and EOS will not be included in the shift tables.

Frequency tabulations of qualitative clinical laboratory variables will be presented by treatment (on/off treatment).

All laboratory data will be displayed in listings.

Laboratory abnormalities that are considered clinically significant (CS) are recorded in the database as AEs. Therefore, no tabulation of laboratory values meeting any CS criteria will be presented as all relevant information will be presented in the AE summaries.

Results of pregnancy tests (females only), serology, alcohol and drug of abuse tests will be listed only.

4.12.4 Vital Signs

A by-participant listing of all vital sign measurements (including weight) and change from baseline will be presented.

Baseline will be defined in section 4.2.4.

Measured (observed) values including changes from baseline will be summarized by on/off treatment and by vital sign parameter (pulse rate, systolic and diastolic blood pressure, and oral body temperature).
Individual clinically significant vital sign values that were considered AEs by the PI will be presented in the AE listings.

4.12.5 12-lead ECG

Standard 12-lead ECG will be obtained as outlined in the SoA (Table 6-1) using an ECG machine that automatically calculates the heart rate. All ECGs in this study should all be recorded using the same make of ECG device (Mortara Surveyor Telemetry Central and Mortara telemetry transmitters Model: Surveyor S4), with the exception of Screening visit, where CardioSoft® will be used. The Mortara system is validated every 12 months. Monitors will also be available to spot check the calibration when on-site. The readings generated by Mortara surveyor S4 machine will be validated by the cardiologist with their interpretation on whether the findings are significant and related to paroxetine. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable Baseline. ECGs will be performed and recorded in the eCRF at the times shown in SoA (Table 6-1). The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, blood sampling, and any remaining assessments for that visit.

At Screening, participants will be excluded based on ECG measurements if the resting QTc is >450msec (mean of three twelve-lead ECG measurements and using Fridericia's correction). The Fridericia QT correction formula (QTcF) must be used for clinical decisions, e.g., at Screening to assess eligibility. Further, all ECGs will be performed in triplicate collected within 5 min, at least 1 minute in between, at each timepoint.

- Triplicate ECGs will be performed at each timepoint as detailed in SOA (Table 6-1). The mean QTc value will be calculated from the triplicate ECGs for each participant.

- The ECG extractions will be paired with paroxetine concentration samples but will be obtained before the actual paroxetine concentration sampling time to avoid changes in autonomic tone associated with the psychological aspects of blood collection as well as the reduction in blood volume subsequent to blood collection.

- At visits where an ECG is not scheduled, an ECG can be performed if medically indicated.

- All ECG traces will be measured by a third-party vendor, which includes review by a licensed cardiologist. The cardiologist will review the ECGs and provide interpretation on whether the findings are normal, abnormal but non-clinically significant , or abnormal but clinically significant.
- A qualitative interpretation of the ECG will be performed by the cardiologist (according to the charter referenced as "Charte_Cardiabase_v5.7_2019-02-12_AtriumV7"). This morphological interpretation will provide a codification of the abnormalities detected on the recordings according to a code list grouping the abnormalities such as Q or Qs pattern, T/U wave abnormalities, Rhythm, etc.
- More than one cardiologist from the vendor may be reviewing the ECGs in the study. However, to remove bias all ECGs of a particular participant will be reviewed by the same cardiologist. The cardiologists will also be blinded to study visits/timestamps/paroxetine dose at which the ECGs were performed. A copy should be filed in the participant's medical records. Any clinically significant finding observed on the ECG should be recorded as an AE. A copy of ECG traces (with participant-identifying details redacted) may be collected by a Sponsor appointed representative for additional cardiology review if required. Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or adverse events as appropriate.

The ECG will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'. All ECG parameters will be listed by participant including changes from baseline.

Baseline is defined in section 4.2.4.

If ECGs measurements are performed in triplicate, then mean of the triplicates will be presented in the listing and used for deriving baseline and changes from baseline.

Descriptive statistics for absolute values and changes from baseline will be presented by visit/ dose level and time point. Two-sided 90% confidence interval of the mean will also be calculated on changes from baseline.

Time course of mean changes from baseline with 90% confidence interval of the mean will be presented by dose level.

A summary of the number and percentage of participants per visit/dose level with ECG intervals exceeding some predefined limits (eg, >450 msec, >480 msec, >500 msec for measured values as well as. >30 msec, >60 msec for changes from baseline for QTc intervals will be displayed in a frequency table. All thresholds for the categorical analysis are presented in Section 6.4. Values meeting the thresholds for abnormality will be flagged in the individual data listings.

A summary of the number and percentage of participants per visit/dose level with at least one treatment emergent morphological abnormality will be displayed in a frequency table. Treatment-emergent abnormality will be defined as any abnormality not already reported on any of the baseline ECGs.

The listing of ECG abnormalities will be presented separately.

The listing of morphological ECG abnormalities will be presented separately.

If ECGs measurement are performed in triplicate, only the mean of the triplicates will be presented in the listing and used for deriving baseline and change from baseline.

4.12.6 Columbia-Suicide Severity Rating Scale

As part of the screening procedures, a Columbia Suicide Severity Rating Scale (C-SSRS) will be performed, to assess the risk of suicidal ideation by the prospective participant. Those who show a risk of suicidal ideation will not be included in the study.

The C-SSRS may be repeated during the study at the discretion of the PI.

4.12.7 Physical Examination

Physical examinations will be performed as shown in section 6.1.

A complete physical examination will include, at a minimum, assessments of the (cardiovascular, respiratory, gastrointestinal, and neurological) systems. Height (at screening) and weight (at screening and discontinuation) will also be measured and recorded. Further, BMI will be calculated from height and weight, and recorded.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

After screening, any clinically significant abnormal findings in physical examinations should be reported as AEs.

4.12.8 COVID-19 Assessment and COVID-19 AEs

The overall incidence of AEs and SAEs of COVID-19, COVID-19 AEs leading to study intervention discontinuation will be summarized.

4.12.9 Other Analysis

Not Applicable.

4.12.10 Daylight Saving Time (DST):

All scheduled times in ClinBase will be automatically updated to ensure a consistent and protocol-compliant period from the scheduling medication to the actual time point.

4.12.11 Safety Monitoring (Independent Data Monitoring Committee, Data Monitoring Committee, Data and Safety Monitoring Board)

An Independent Data Monitoring Committee (IDMC) is not required for this study.

4.13 Handling of Dropouts or Missing Data

No imputation of missing data will be performed except for partial dates imputation mention in Section 6.2.

4.14 Subgroup Analysis

No subgroup analysis is planned for this study.

4.15 Planned Interim Analyses

No interim analysis is planned for this study.

4.16 Determination of Sample Size

At least 36 participants, men or non-pregnant women, aged 18 to 65 years will be enrolled. This number is expected to result in sufficiently wide range of paroxetine concentrations to cover those typically observed in a real-world clinical setting. A Monte Carlo simulation analysis was used to determine the probability of the 90% upper limit of the CI of the ΔQTC at the geometric mean of the 60 mg dose encompassing the 10 ms cut-off value. Based on this simulation approach, it is expected that under the assumption of no true effect of paroxetine on QTc at the 60 mg dose, the expected probability of incorrectly detecting an effect (90% upper limit of the CI ≥10 ms) is <1% (false positive) when inclusion is 36 participants. In case the true effect is 5 ms, the expected probability of a false positive is <2%. When the true effect is 10 ms, the expected probability of
correctly determining a QTc prolongating effect is approximately 82%.

The sensitivity to missing data was also assessed. With 20% drop out at the 40 mg dose and another 25% drop out at the 60 mg dose (in addition to the drop out at the 40 mg dose) the expected probability of incorrectly detecting an effect (90% upper limit of the CI 10 msec) for 36 participants is 1% (false positive) when the true effect is null. The expected probability of a false positive is 5% if the true effect is 5 msec. The expected
probability of correctly determining a QTc prolonging effect is approximately 85% when the true effect is 10 msec.

The sensitivity of the probability of correctly determining a QTc prolonging effect is calculated with respect to different sample sizes (20, 30, 36, 46, 56) and assuming true effect as 0 msec, 5 msec, and 10 msec.

Sample Size Sensitivity without dropout

True effect	**0 msec**	**5 msec**	**10 msec**
N	**Probability of the upper 90% limit of model-predicted ΔQTc being ≥10 msec**		
20	0	4.3	80.3
30	0	1.8	82.8
36	0	0.6	82.5
46	0	0.4	84.2
56	0	0.1	85.3

The sensitivity of the probability of correctly determining a QTc prolonging effect is calculated with respect to different sample sizes (20, 30, 36, 46, 56) and assuming true effect as 0 msec, 5 msec, and 10 msec. Additionally, it incorporates a 20% drop out at the 40 mg dose and another 25% drop out at the 60 mg dose (in addition to the drop out at the 40mg dose).

Sample Size Sensitivity after drop-out

True effect	0 msec	5 msec	10 msec
N	**Probability of the upper 90% limit of model-predicted ΔQTc being ≥10 msec**		
20	0.6	15.3	80.5
30	0	8.7	83.3
36	0	4.9	85.1
46	0	3.6	86.1
56	0	1.2	84

4.17 Changes in the Conduct of the Study or Planned Analysis

The following changes are made in this study to the planned analysis in study protocol.

4.17.1 Change in analysis sets defined in protocol section 9.2 – Analysis sets:

Analysis set defined in protocol	Analysis set defined in SAP	Rationale
Enrolled analysis set - All participants who entered the study (who received study intervention)	Enrolled analysis set - All participants who entered the study (who successfully passed screening)	To collect the data from all participants who passed Screening

5 REFERENCES

[1] SAS® Version 9.4 of the SAS System for Personal Computers. Copyright ©2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

[2] Phoenix®WinNonlin® Software Version 8.3. https://www.certara.com

[3] Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018;45(3):383–97

[4] GSK Non-Compartmental Analysis of Pharmacokinetic Data (VQD-GUI-000722 (6.0))

[5] Koch HJ & Raschka C. Ultradian diurnal variations of QTc and relevant cardiovascular characteristics should be considered awith regard to risk assessment. European Heart Journal (2002) 23, 341–342

6 APPENDICES

6.1 Schedule of Activities

Figure 2 Schedule of Activities - Overview Across Visit Days

Procedures	Screening		Baseline	Treatment Period and Exit Visit1										Early Discontinuation / Withdrawal Visit	Follow-up / End of Study
Study Visit	**1**		**2**	**2**	**3**			**4**			**5**			**Discontinue / Withdrawal Visit**	**6**
Study Day	**-28 to -31**	**-2**	**-1**	**1**	**6**	**7**	**8**	**13**	**14**	**15**	**20**	**21**	**22**	**–**	**Up to 14 days after last dose**
Informed consent[2]	X														
Inclusion/Exclusion criteria[2]	X		X												
Demography/childbearing status assessment	X														
Medical and treatment history	X														
Brief physical examination including height and weight[3]	X[3]			X		X			X			X		X	X
Arrive in clinic evening before Visit day[4]		X[5]	X		X			X			X				
Dosing in clinic[6]				X		X	X		X	X		X			

Procedures	Screening		Baseline	Treatment Period and Exit Visit1									Early Discontinuation / Withdrawal Visit	Follow-up / End of Study
Study Visit	**1**		**2**	**2**	**3**			**4**			**5**		**Discontinue / Withdrawal Visit**	**6**
Study Day	**-28 to -31**	**-2**	**-1**	**1**	**6**	**7**	**8**	**13**	**14**	**15**	**20**	**21**	**22**	**–**	**Up to 14 days after last dose**
Receive first of next dose level in clinic[7]				X			X			X					
AE/SAE assessment[8]	←												→		
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X		X	X
Vital signs[9, 10]	X		X	X	X	X	X	X	X	X	X	X		X	X
ECG[10, 11]	X		X[12]			X[12]			X[12]			X[12]		X[12]	X[12]
Paroxetine concentrations[10, 11]			X			X			X			X			
Haematology with differential[10]	X													X	X
Clinical and renal/liver chemistry[10]	X													X	X
Pregnancy test, alcohol and drug of abuse tests[10, 13]	X		X		X			X			X			X	X
FSH test [14]	X														
COVID-19 test[15]	X		X		X			X			X			X	X

Procedures	Screening		Baseline	Treatment Period and Exit Visit1									Early Discontinuation / Withdrawal Visit	Follow-up / End of Study
Study Visit	**1**		**2**	**2**	**3**			**4**			**5**		**Discontinue / Withdrawal Visit**	**6**
Study Day	**-28 to -31**	**-2**	**-1**	**1**	**6**	**7**	**8**	**13**	**14**	**15**	**20**	**21**	**22**	**–**	**Up to 14 days after last dose**
Serology (HIV, HBV, and HCV)	X														
C-SSRS	X														
Discharge[16]				X			X			X		X[17]	X[17]		
Complete eCRF (ClinBase)			X[18]	X[18]		X[18]			X[18]			X[18]		X	X

Abbreviations: AE, adverse event; C-SSRS, Columbia suicide severity rating scale; ECG, electrocardiogram; eCRF, electronic case report form; SAE, serious adverse event.

1. All participants will need to attend a clinic visit at Screening (Visit 1), Baseline (Visit 2, Day-1) and first 20 mg dose (Visit 2, Day 1), assessment at 20 mg steady-state dose (Visit 3, Day 7), first 40 mg dose (Visit 3, Day 8), assessment at 40 mg steady-state dose (Visit 4, Day 14), first 60 mg dose (Visit 4, Day 15) assessment at 60 mg steady-state dose and exit visit (Visit 5, Day 21) . They will also attend the clinic for the final follow-up visit (Visit 6). Participants will receive a follow-up video-call from the unit on all other dosing days outside of the clinic and the 3 days after last dose, and will take tablets under supervision of clinical staff over video-call.
2. Informed consent and eligibility criteria assessment data will all be captured on site. Informed consent must be obtained prior to starting screening procedures.
3. Height will be measured at Screening only. Complete physical examination will be performed at Screening and final Follow-Up Visit, and brief physical examination at all further visits.
4. Participants will arrive at clinic in the evening (~20:00 PM) before the visit day (at Baseline [Day -1], Visit 2 [Day 6], Visit 4 [Day 13], and Visit 5 [Day 20]).
5. Participants need to come in the evening on Day -2 and stay overnight for procedures on Day -1.
6. On Visit 3 (Day 7), 4 (Day 14) and 5 (Day 21), the current (at that time) dose of paroxetine will be taken by the participant under supervision of staff.
7. For Study Days 1 (Visit 2, 20 mg), Day 8 (Visit 3, 40 mg) and Day 15 (Visit 4, 60 mg), the participant will take the first dose of the next dose level (20, 40 and 60 mg respectively) under supervision of staff, remaining under observation for 3 hours post-dose and will be discharged afterwards.
8. SAEs must be collected from signing of informed consent if considered related to study procedures.

9. Vital sign measurements will include oral body temperature, systolic and diastolic blood pressure (BP), and pulse rate. Triplicate BP measurements will be performed in supine position at Screening only.
10. Vitals, laboratory assessments (coagulation parameters, haematology with differential, clinical and liver chemistry, pregnancy test, and paroxetine concentrations samples) and ECG data will all be captured at visits on site. During the treatment period, all laboratory samples and vitals (including one paroxetine concentration sample) should be obtained pre-dose.
11. All ECGs will be performed in triplicate collected within 5 min at each timepoint. ECG triplicates will be performed once at Screening (Visit 1), and at Follow-Up Visit and at discontinuation or withdrawal visits. At Visits 2 (Day -1), 3 (Day 7), 4 (Day 14), and 5 (Day 21) ECG triplicates will be performed 15 min pre-dose (-0.25 h) and post-dose at the following timepoints 1, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 10, 12h. Each ECG triplicates will be combined with paroxetine concentration assessment. Paroxetine concentrations at Visits 3 (Day 7), 4 (Day 14), and 5 (Day 21) will be procured at the following timepoints: -0.25, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 10, 12 h. One sample will be collected for paroxetine concentrations on Day -1 at 0.25h (pre-dose). The paroxetine dose should be taken at the same clock time each time, at a time approximately between 07:00-010:00 (7to 10 am). When scheduled for the same time, ECGs should be performed before blood sampling to avoid impact on ECG parameters.
12. .
13. At Visits 2 (Day -1), 3 (Day 7), 4 (Day 14), and 5 (Day 21), follow-up visit and at discontinuation or withdrawal visits, serial ECG review will be performed by Mortara system.
14. Negative urine pregnancy test result must be confirmed prior to dosing in female participants of reproductive potential. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
15. FSH test be performed for postmenopausal women only.
16. COVID-19 testing will be performed as per site practice.
17. Participants will be discharged from the clinic 3 hours after the morning dose on Study Days 1, 8, and 15 (Visit 2, 3, 4) to subsequently take paroxetine doses at home until the next Visits in clinic.
18. Participants will get discharge on either Day 21 or Day 22 (may stay overnight) as per the convenience.

The date and time of the administration of study intervention will be recorded in the eCRF. N.B. participants will be provided with the required tablets for dosing up to the next visit. Participants will take the tablet(s) under supervision when in the clinic, and under video-call supervision when outside the clinic

6.2 Imputation Rules for Partial Dates

Imputed dates and time will NOT be presented in the listings.

Table 6-2 and Table 6-3 present algorithm for age derivation, imputing partial dates for AE, TEAE and prior/concomitant medication respectively.

Table 6-2 Age Derivation

Age Derivation
Age will be calculated based on the Pre-Screening Visit date (or Screening, if pre-screening not performed). Only year of birth is collected on eCRF. Day and Month of birth are imputed as 30 June. Age is derived using the date of the screening visit. Birth date will be presented in listings as 'YYYY'.

Table 6-3 Handling of Partial Dates

Element	Reporting Detail	
General	Partial dates will be displayed as captured in participant listing displays. Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.	
Adverse Events	Partial dates for AE recorded in the CRF will be imputed using the following conventions:	
	Missing start day	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month. Else if study intervention start date is not missing: If month and year of start date = month and year of study intervention start date, then If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month. Else set start date = study intervention start date. Else set start date = 1st of month.
	Missing start day and month	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: If year of start date = year of study intervention start date, then If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. Else set start date = study intervention start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).

Element	Reporting Detail	
	Missing end day and month	No Imputation
	Completely missing start/end date	No imputation
Concomitant Medications/Medical History	Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:	
	Missing start day	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month. Else if study intervention start date is not missing: If month and year of start date = month and year of study intervention start date, then If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month. Else set start date = study intervention start date. Else set start date = 1st of month.
	Missing start day and month	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: If year of start date = year of study intervention start date, then If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. Else set start date = study. intervention start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation

6.3 Laboratory Test Parameters

Laboratory Tests	Parameters	
Hematology	• Platelet count	
	• Red blood cell (RBC) count	
	• RBC indices	○ Mean corpuscular volume (MCV) ○ %Reticulocytes
	• WBC count with differential:	○ Neutrophils ○ Lymphocytes ○ Monocytes ○ Eosinophils ○ Basophils
	• Haemoglobin	
	• Haematocrit	
Clinical chemistry	• Potassium • Creatinine • Sodium • Calcium	○ Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) ○ Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) ○ ALP ○ Bilirubin (total, direct and indirect) ○ Creatinine kinase
Coagulation tests	• Prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ration (INR),	
Pregnancy testing	• Highly sensitive serum at screening and final follow-up visit and urine on admission human chorionic gonadotropin (hCG) pregnancy test as needed for WOCBP	
Other screening tests	• Follicle stimulating hormone and oestradiol (as needed in WONCBP only) • Urine alcohol and drug screen to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines, urine creatinine	

	• Serology HIV antibody and p24 antigen test, HBsAg, and HCV antibody.

1. All events of ALT [or AST] ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (> 35% direct bilirubin) or ALT [or AST] ≥3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to [Sponsor] in 24 hours (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. Local urine testing at screening will be standard for the protocol unless serum testing at screening is required by local regulation or IRB/IEC.

6.4 ECG Notable Criteria

Parameter	Definition/threshold	Flag for listings
QTcF, QTcB (msec)	QTc Value >450 and ≤480 msec	B
	QTc value >480 and ≤500 msec	H
	QTc value >500 msec	P
	QTc increase > 30 and ≤60 msec	I
	QTc increase>60 msec	I+
HR (beats/min)	HR<40 beats/min	L
	HR>120 beats/min	H
	HR relative change >25%	I
PR (msec)	PR>220 msec	H
	PR relative change >25%	I
QRS (msec)	QRS relative change >25%	I
	QRS>120 msec	H

Flagging system will be used in listings to identify values meeting thresholds, also not necessarily related to clinically significant events, the flags can be interpreted as follows:
L: Low value - B: Borderline value - H: High value - P: Prolonged value
I: Noticeable increase from baseline - I+: marked increase from baseline.
QTc correspond to both QTcF and QTcB

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PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: F76AC045-6175-4BAF-A736-C51EA3FBF504 Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 12/5/2023 7:24:10 AM Viewed: 12/6/2023 8:30:44 PM Signed: 12/7/2023 3:37:07 AM
Electronic Record and Signature Disclosure: Accepted: 10/2/2023 10:37:09 PM ID: e5ed34aa-5196-44e4-b034-67445dda0578		
PPD Security Level: Email, Account Authentication (Required)	DocuSigned by: PPD Signer Name: PPD Signing Reason: I am the author of this document Signing Time: 12/5/2023 | 8:44:36 AM PST 2B2AA041BAB0496EA323C64E64D89337 Signature Adoption: Pre-selected Style Signature ID: 2B2AA041-BAB0-496E-A323-C64E64D89337 Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 12/5/2023 7:24:11 AM Viewed: 12/5/2023 8:42:27 AM Signed: 12/5/2023 8:44:46 AM
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Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	DocuSigned by: PPD Signer Name PPD Signing Reason: I approve this document Signing Time: 12/6/2023 | 8:07:10 AM PST 297C0EA0E4F74C02B9C041860131E1B7 Signature Adoption: Pre-selected Style Signature ID: 297C0EA0-E4F7-4C02-B9C0-41860131E1B7 Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 12/5/2023 7:24:12 AM Viewed: 12/6/2023 8:06:10 AM Signed: 12/6/2023 8:07:15 AM
Electronic Record and Signature Disclosure: Accepted: 12/6/2023 8:06:10 AM ID: 8b74d965-08f3-4af0-bd64-dd0b6d2f7a49		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: 64946B0D-9036-4C14-BEB6-CB97F5547617 Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 12/5/2023 7:24:12 AM Viewed: 12/6/2023 2:08:11 AM Signed: 12/6/2023 2:08:37 AM
Electronic Record and Signature Disclosure: Accepted: 11/29/2023 12:04:00 AM ID: 97b1f128-1d36-4b6b-93a0-b07f99401401		
PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: E66EDFC8-2E4C-437C-85DD-02380EFE5FEE Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 12/5/2023 7:24:13 AM Viewed: 12/5/2023 10:31:52 AM Signed: 12/5/2023 10:33:17 AM
Electronic Record and Signature Disclosure: Accepted: 9/13/2023 5:26:27 AM ID: 3844bf0d-b5cc-4bca-ab40-3aae8d4b0a1d		

Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required)	DocuSigned by: PPD Signer Name PPD Signing Reason: I approve this document Signing Time: 12/7/2023 | 1:43:38 AM PST AC5F46252EF94BD0B1FE22986B4022DE Signature Adoption: Pre-selected Style Signature ID: AC5F4625-2EF9-4BD0-B1FE-22986B4022DE Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 12/5/2023 7:24:14 AM Viewed: 12/6/2023 9:16:05 AM Signed: 12/7/2023 1:43:46 AM
Electronic Record and Signature Disclosure: Accepted: 12/6/2023 9:16:05 AM ID: 05d8ce1f-a531-450c-8cfe-7f28cd5bc5e8		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	12/5/2023 7:24:14 AM
Certified Delivered	Security Checked	12/6/2023 9:16:05 AM
Signing Complete	Security Checked	12/7/2023 1:43:46 AM
Completed	Security Checked	12/7/2023 3:37:07 AM

Payment Events	Status	Timestamps

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