Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	A Study to Evaluate the Effect of Therapeutic and Supratherapeutic Oral Doses of GSK3640254 on Cardiac Conduction as Assessed by 12-Lead Electrocardiogram Compared to Placebo and a Single Oral Dose of Moxifloxacin in Healthy Adult Participants
Compound Number	:	GSK3640254
Effective Date	:	01/07/2021

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 213053.
- This RAP is intended to describe the full analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol: 213053.

2. SUMMARY OF KEY PROTOCOL INFORMATION

This is a 2-part study. Part 1 is a sequential treatment study with 2 arms that is participant and investigator blinded. Part 2 is a single group, single arm, crossover treatment study that is participant and investigator blinded (open-label for moxifloxacin).

2.1. Changes to the Protocol Defined Statistical Analysis Plan

None.

2.2. Study Objective(s) and Endpoint(s)

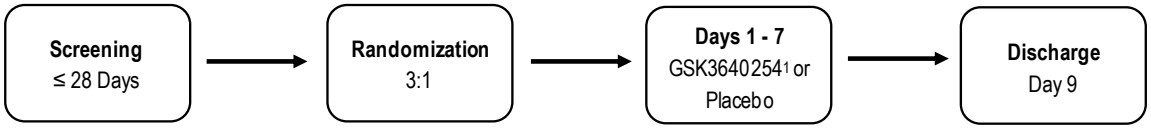
Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
Part 1: • To determine the safety and pharmacokinetics of a supratherapeutic dose of GSK3640254 administered for 7 days in healthy participants	Part 1: • Area under the plasma concentration-time curve from time zero to time t (AUC[0-t]), area under the plasma concentration-time curve from time zero to the end of the dosing interval at steady state (AUC[0-τ]), maximum observed concentration (Cmax), plasma concentration at the end of the dosing interval (Cτ), and time of maximum observed concentration (Tmax) of GSK3640254 in plasma • Remaining plasma will be analysed for compound related metabolites • Safety and tolerability parameters for adverse events (AEs)/serious adverse events (SAEs), observed and change from baseline in clinical laboratory assessments, electrocardiograms (ECGs), and vital sign measurements
Part 2: • To determine the effect of therapeutic and supratherapeutic concentrations of multiple dose GSK3640254 on the QT interval corrected with Fridericia's formula (QTcF) in healthy participants	Part 2: • Placebo-corrected change from baseline in QTcF (ΔΔQTcF) for GSK3640254 using concentration-QTc (C-QTc) analysis (primary analysis) • Remaining plasma will be analysed for compound related metabolites

Secondary Objectives	Secondary Endpoints
Part 2: • To evaluate the effect of multiple oral therapeutic and supratherapeutic doses of GSK3640254 on other ECG parameters (heart rate [HR], PR, QRS, and QTcF intervals, treatment-emergent T-wave morphology, and appearance of U-waves)	Part 2: • Change from baseline in HR, QTcF, PR, QRS (ΔHR, ΔQTcF, ΔPR, and ΔQRS) intervals using by-time point analysis (secondary analysis); the placebo-corrected change from baseline in HR, PR, QTcF, and QRS (ΔΔHR, ΔΔPR, ΔΔQTcF, and ΔΔQRS) using by-time point analysis; categorical outliers for QTcF, HR, PR, and QRS; and the frequency of treatment emergent changes of T-wave morphology and U-wave presence
• To demonstrate assay sensitivity of the study design to detect a QTc effect using a single dose of 400 mg oral moxifloxacin as a positive control.	• ΔΔQTcF for moxifloxacin (primary: C-QTc analysis and secondary: by-time point analysis)
• To evaluate the pharmacokinetics of multiple oral therapeutic and supratherapeutic doses of GSK3640254 and a single dose of moxifloxacin.	• AUC(0-t), AUC(0-τ), Cmax, Cτ, and Tmax of GSK3640254 in plasma • Cmax and Tmax of moxifloxacin in plasma
• To assess the safety and tolerability of multiple therapeutic and supratherapeutic doses of GSK3640254	• Safety and tolerability parameters for AEs/SAEs, observed and change from baseline in clinical laboratory assessments, ECGs, and vital sign measurements

2.3. Study Design

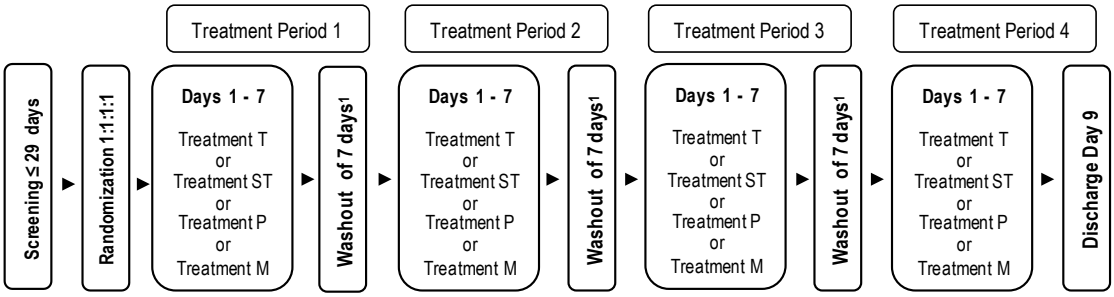
Overview of Study Design and Key Features

Figure 2.3.1 Study Design Schematic – Part 1



1. Sentinel Cohort 1: GSK3640254 500 mg or placebo once daily.
   Sentinel Cohort 2 (if needed): GSK3640254 or placebo twice daily, with only a single morning dose administered on the seventh day; dose to be determined after completion of Sentinel Cohort 1.

Figure 2.3.2 Study Design Schematic – Part 2



1. Washout will be at least 7 days minus 4 hours to allow for flexibility in scheduling in the clinic.

Treatment T: Therapeutic dose of GSK3640254 (100 mg once daily) Days 1 through 7.
Treatment ST: Supratherapeutic dose of GSK3640254 (to be determined from Part 1) Days 1 through 7
Treatment P: Placebo for GSK3640254 Days 1 through 7.
Treatment M: Moxifloxacin; GSK3640254 placebo Days 1 through 6 and a single dose of Moxifloxacin (400 mg) on Day 7

Design Features	This study has an adaptive 2-part design, where projected doses will be identified and may be modified according to assessment of accrued data. Part 1 will consist of up to 2 sentinel cohorts to determine the supratherapeutic dose for Part 2, which will be the main QTc study.
	
	Part 1 will be a randomized, double-blind study. Part 2 will be a double-blind, randomized, placebo-controlled study. Moxifloxacin is included as a positive control and will be open label.
	• Part 1 of the study will consist of a screening period and a treatment period for each cohort.
	  ○ Sentinel Cohort 1: GSK3640254 500 mg or placebo orally QD for 7 days.
	  ○ Sentinel Cohort 2 (optional): If needed, a dose of GSK3540254 or placebo orally BID for 7 days (13 doses), with only a single morning dose administered on the seventh day. The specific dose in sentinel Cohort 2 will be determined based on the results of preliminary safety and PK data from sentinel Cohort 1 and decided upon by the study team and the investigator.
	  ○ Up to 16 participants may be enrolled (8 participants per cohort)

Overview of Study Design and Key Features

Part 2, Main QTc Study:

Part 2 of the study will consist of a screening period, a check-in visit (Day -2), a baseline visit (Day -1), and 4 sequential treatment periods. Participants will receive treatments in 1 of the 12 following sequences:

Sequence	Period 1	Period 2	Period 3	Period 4
1	T	ST	P	M
2	ST	M	T	P
3	P	T	M	ST
4	M	P	ST	T
5	ST	P	T	M
6	P	M	ST	T
7	T	ST	M	P
8	M	T	P	ST
9	P	T	ST	M
10	T	M	P	ST
11	ST	P	M	T
12	M	ST	T	P

Treatment T: Therapeutic dose of GSK3640254 (100 mg once daily) Days 1 through 7.
Treatment ST: Supratherapeutic dose of GSK3640254 (to be determined from Part 1) Days 1 through 7.
Treatment P: Placebo for GSK3640254 Days 1 through 7.
Treatment M: Moxifloxacin; GSK3640254 placebo Days 1 through 6 and a single dose of Moxifloxacin (400 mg) on Day 7.
To maintain the blind, the number of tablets administered for therapeutic, supratherapeutic, moxifloxacin (Days 1 through 6 only), and placebo doses will be identical. The total number of tablets will be based on the actual supratherapeutic dose derived from Part 1 of the study. For example, if the supratherapeutic dose is determined to be 500 mg QD, the therapeutic dose would consist of one 100 mg GSK3640254 tablet and four placebo tablets, the supratherapeutic dose would consist of five 100 mg GSK3640254 tablets, and the placebo dose would consist of five placebo tablets.

Approximately 42 participants will be enrolled to achieve 34 evaluable participants.

Dosing

Intervention	GSK3640254	GSK3640254 Placebo	Moxifloxacin
Type	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Capsule
Unit Dose Strength	100 mg	N/A	400 mg
Dosage Levels	Therapeutic: 100 mg Supratherapeutic: TBD	N/A	400 mg
Route of Administration	Oral	Oral	Oral

IMP = investigational medicinal product; NIMP = non-investigational medicinal product;

Overview of Study Design and Key Features	
	TBD = to be determined.
Time & Events	• Refer to Appendix 1: Schedule of Activities
Treatment Assignment	• Part 1: up to 2 sequential cohorts of approximately 8 healthy participants each (3:1 ratio to receive GSK3640254 or placebo). • Part 2: Approximately 42 participants will be randomized to ensure 34 evaluable participants with data from all treatment periods. Participants will be randomly assigned to 1 of 12 treatment sequences in Part 2 of Design Features.
Interim Analysis	• No interim analysis is planned for this study

2.4. Statistical Hypotheses

There is no formal hypothesis that will be statistically tested in Part 1 of this study.

For Part 2, the statistical hypothesis to be tested for the primary assessment of QT prolongation at the highest clinically relevant exposure using the C-QTc analysis for each active dose group is:

H_0: $\Delta\Delta QTc \geq 10$ ms

H_1: $\Delta\Delta QTc < 10$ ms

where ΔΔQTc is the mean ΔΔQTc (primary endpoint) at the mean Cmax for each active dose group, respectively.

In addition, the statistical hypothesis to be tested for the assay sensitivity using the C-QTc analysis is:

H_0: $\Delta\Delta QTc \leq 5$ ms

H_1: $\Delta\Delta QTc > 5$ ms

where ΔΔQTc is the mean ΔΔQTc (primary endpoint) at the mean Cmax for the moxifloxacin group.

2.5. Sample Size Determination

Part 1: A total of up to 16 participants are planned to be randomized, 8 participants per cohort (6 participants to receive GSK3640254 and 2 participants to receive placebo). For Part 1, as there is no formal research hypothesis being statistical tested, the sample size is not selected based on statistical considerations but was determined using feasibility.

Part 2: A sample size of approximately 42 participants is chosen to obtain 34 evaluable participants to complete the study. A sample size of 34 evaluable participants will provide more than 90% power to exclude that active drug causes more than a 10-ms QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% CI of the model predicted QTc effect (ΔΔQTc: primary endpoint) at the observed geometric mean Cmax of active drug in the study.

This power is estimated approximately using a paired t-test. The calculation assumes a one-sided 5% significance level, an underlying effect of GSK3640254 of 4 ms and a standard deviation (SD) of the ΔQTc of 8.5 ms for both active drug and placebo. Table 1 provides the sample sizes for power of 90% and 95% with underlying effect of 3, 4, and 5 ms and SD of 8, 8.5 and 9.5 ms.

The C-QTc analysis method is supported by Darpo, 2015 and Ferber, 2015, and consistent with the experiences from 25 recent TQT studies in ERT, which provided SD=8 ms as a conservative estimate for general TQT studies. Note that this calculation is conservative also because it does not take into account any gain in precision due to the use of all data of each subject with the help of a linear mixed effects model. An SD of 9.5 ms is a conservative value used in previous MI compound BMS-663068 and AI compound Fostemsavir TQT studies in GSK. In the previous GSK3640254 first time in human study 207187 SAD/MAD study, the within-subject SD based on by-time point analysis is 8.5 ms, which provides the conservative estimated SD for this compound. Therefore, the underlying effect 4 ms and SD=8.5 ms with 90% of power for the study sample size of 34 participants was chosen for this study. With the dropout rate of 20%, approximately 42 participants will be enrolled to ensure the evaluable number of participants is greater or equal to 34.

Table 1 Sample Size Determination - Power

Sample size	Number of Participants for 90% Power	Number of Participants for 95% power
Underlying effect 3 ms, SD = 8 ms	22	28
Underlying effect 3 ms, SD = 8.5 ms	25	32
Underlying effect 3 ms, SD = 9.5 ms	32	40
Underlying effect 4 ms, SD = 8 ms	30	38
Underlying effect 4 ms, SD = 8.5 ms	34	43
Underlying effect 4 ms, SD = 9.5 ms	43	54
Underlying effect 5 ms, SD = 8 ms	44	55
Underlying effect 5 ms, SD = 8.5 ms	49	63
Underlying effect 5 ms, SD = 9.5 ms	62	78

Sample Size for Assay Sensitivity: To demonstrate assay sensitivity with C-QTc analysis, it must be shown that the ΔΔQTc of a single dose of 400 mg moxifloxacin exceeds 5 ms (i.e., the lower bound of the 2-sided 90% CI of the predicted QTc effect [ΔΔQTc: primary endpoint] should exceed 5 ms).

In a similarly designed, recent crossover study with 24 healthy participants (on-file data, ERT), the standard error (SE) for the prediction of the QT effect of moxifloxacin based on the C-QTc analysis was 1.24 ms. The within-subject SD of ΔQTcF in this study was 5.4 ms based on the by-time point analysis. If the effect of moxifloxacin is assumed to be 10 ms, the SE of 1.24 ms corresponds to an effect size of (10-5)/(1.24×sqrt[24])=0.82, where the effect size is the effect assumed under the alternative hypothesis divided by the SD of the test variable. This value should be compared to the effect size of 0.62 required to guarantee a power of at least 95% in a paired *t*-test situation with a sample size of

30 evaluable participants. In other words, based on this calculation, a power of at least 95% for 30 evaluable participants will be obtained as long as the variability of the ΔQTc, as measured by its within-subject SD, does not exceed 7.1 ms (i.e., 132% of the 5.4 ms observed in the above referenced study [on-file data, ERT] assuming the ratio of effective sizes is consistent with inverse ratio of within-subject SD). The number also agrees with recent recommendations of the FDA, which propose at least 20 participants (Huang, 2019).

3. PLANNED ANALYSES

3.1. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) have been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who signed the informed consent form	• Study Population
Randomized	• All participants who are randomly assigned to a treatment/treatment sequence.	• Disposition
Safety	• All randomized participants who receive at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.	• Demographic • Safety
QT/QTc	• All participants in the safety population with measurements at baseline as well as on-treatment with at least 1 post-dose time point with a valid ΔQTc value.	• By-time point and categorical analyses of the cardiodynamic ECG parameters
Pharmacokinetic Concentration	• All participants who undergo plasma PK sampling and have evaluable PK assay results.	• PK Concentration
Pharmacokinetic Parameter	• All participants who undergo plasma PK sampling and have evaluable PK parameters estimated.	• PK Parameter • PK statistical analysis
PK/QTc	• All participants who are in both the QT/QTc and PK concentration populations with at least 1 pair of post-dose PK and ΔQTc data from the same time point as well as participants in the QT/QTc population who received placebo. The PK/QTc Population will be defined for GSK3640254 and for moxifloxacin.	• C-QTc analysis and assay sensitivity

Refer to Appendix 9: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, participant management or participant assessment) will be summarized and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Study Deviation Tool and Rules. The "significant" protocol deviation in the Study Deviation Tool and Rules is equivalent to "important" protocol deviations.

- Data will be reviewed prior to freezing the database to ensure all significant deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This listing will be based on data as recorded on the inclusion/exclusion page of the electronic case record form (eCRF).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions		
Data Displays for Reporting		
Description	**Code**	**Order in TLF**
Part 1		
Placebo	Placebo	1
GSK3640254 500 mg orally QD for 7 days	Treatment A	2
	Treatment B	3
Part 2		
Placebo for GSK3640254 Days 1 through 7.	Placebo	4
Moxifloxacin; GSK3640254 placebo Days 1 through 6 and a single dose of Moxifloxacin (400 mg) on Day 7.	Treatment M	5
Therapeutic dose of GSK3640254 (100 mg once daily) Days 1 through 7.	Treatment T	6
Supratherapeutic dose of GSK3640254 500 BID Days 1 through 7.	Treatment ST	7

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions), baseline for Part 1 is defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits; Baseline for Part 2 is defined as the latest pre-dose assessment with a non-missing value for each period, including those from unscheduled visits.

Part 1:

Parameter	**Study Assessments**			**Baseline Used in Data Display**
	Check-in (Day -2)	**Day -1**	**Day 1 (Pre-Dose)**	
Vital Sign	X	X	X	Day 1 (Pre-Dose)[1]
12-Lead ECG	X	X	X	Day 1 (Pre-Dose)[1]
Hematology	X			Check-in Day -2
Clinical Chemistry	X			Check-in Day -2
Urinalysis	X			Check-in Day -2

[1] The average (for blood pressure and pulse) or the worst case (for interpretation) of the pre-dose triplicate assessments will be used as the baseline.

Part 2:

Parameter	Study Assessments					Baseline Used in Data Display	
	Check-in (Day -2)	Day -1	Periods 1, 2, 3		Period 4 Day 1 (Pre-dose)	Period 1	Period 2, 3, 4
			Day 1 (Pre-dose)	Washout Day 14			
Vital Sign	X	X	X	X	X	Day 1 (Pre-Dose)[1]	Day 1 (Pre-Dose)[1]
12-Lead ECG	X	X	X	X	X	Day 1 (Pre-Dose)[1]	Day 1 (Pre-Dose)[1]
Hematology	X			X		Check-in Day -2	Washout Day 14 for previous period
Clinical Chemistry	X			X		Check-in Day -2	Washout Day 14 for previous period
Urinalysis	X			X		Check-in Day -2	Washout Day 14 for previous period

[1] The average (for blood pressure and pulse) or the worst case (for interpretation) of the pre-dose triplicate assessments will be used as the baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
11.1	Appendix 1: Schedule of Activities
11.2	Appendix 2: Study Phase and Treatment Emergent Adverse Event
11.3	Appendix 3: Data Display Standards & Handling Conventions
11.4	Appendix 4: Derived and Transformed Data
11.5	Appendix 5: Reporting Standards for Missing Data
11.6	Appendix 6: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events
11.7	Appendix 7: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the “Safety”, “Randomized” or “Screened” population, unless otherwise specified.

Study population analyses including analyses of participant’s disposition, protocol deviations (including inclusion/exclusion criteria deviations), demographic and baseline characteristics, prior and concomitant medications, and exposure will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 9: List of Data Displays.

7. PHARMACOKINETIC ANALYSES

7.1. Primary Pharmacokinetic Analyses

7.1.1. Endpoint / Variables

7.1.1.1. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 11.3.3 Reporting Standards for Pharmacokinetics). For Part 1, plasma concentrations of GSK3640254 will be measured and presented in tabular form and will be summarized descriptively. Plasma GSK3640254 concentration-time data will be listed by participant, treatment group, and nominal sampling time and summarized by treatment group and nominal sampling time.

7.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of Phoenix WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. If actual times are missing, nominal times may be used and will be noted in report. Plasma pharmacokinetic parameters listed below will be determined from the plasma concentration-time data, as data permit. Subjects who experience emesis at or before 2 times median T_{max} for the given treatment will be excluded from the calculation of summary statistics and statistical analysis for the respective treatment.

Parameter	Parameter Description
AUC(0-t)	Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-τ)	Area under the plasma concentration-time curve from time 0 to the end of the dosing interval at steady state, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Cτ	Plasma concentration at the end of the dosing interval
Tmax	Time of maximum observed concentration

NOTES:

- Additional parameters may be included as required.

7.1.2. Summary Measure

Pharmacokinetic parameters AUC(0-t), AUC(0-τ), Cmax, Cτ , and Tmax at steady state following administration of GSK3640254 to healthy participants.

7.1.3. Population of Interest

The primary PK analyses will be based on the PK concentration population for plasma PK concentrations and the PK parameter population for plasma PK parameters and statistical analysis.

7.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.1.1 will be summarized using descriptive statistics and listed.

For Part 1, primary plasma PK parameters (AUC[0-t], AUC[0-τ], Cmax, Cτ, and Tmax) will be estimated for GSK3640254. Summary statistics (arithmetic mean, geometric mean, median, standard deviation (SD), coefficient of variation (CV), minimum, maximum, between-subject coefficient of variation (CVb), and 95% confidence interval (CI) for plasma GSK3640254 PK parameter values will be summarized by treatment.

Additionally, pre-dose (trough) PK plasma concentrations of GSK3640254 will be summarized and used to assess achievement of steady state.

7.2. Secondary Pharmacokinetic Analyses

7.2.1. Endpoint / Variables

7.2.1.1. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 11.3.3 Reporting Standards for Pharmacokinetics). For Part 2, plasma concentrations of GSK3640254 and moxifloxacin will be measured and presented in tabular form and will be summarized descriptively. Plasma GSK3640254 and moxifloxacin concentration-time data will be listed by participant, treatment group, and sampling time and summarized by treatment group and sampling time.

7.2.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of Phoenix WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. If actual times are missing, nominal times may be used and will be noted in report.

Plasma pharmacokinetic parameters listed below will be determined from the plasma concentration-time data, as data permit. Subjects who experience emesis at or before 2 times median T_{max} for the given treatment will be excluded from the calculation of summary statistics and statistical analysis for the respective treatment.

Parameter	Parameter Description
AUC(0-t)	Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. (GSK3640254 only)
AUC(0-τ)	Area under the plasma concentration-time curve from time 0 to the end of the dosing interval at steady state, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. (GSK3640254 only)

Parameter	Parameter Description
Cmax	Maximum observed concentration, determined directly from the concentration-time data. (GSK3640254 and moxifloxacin)
Cτ	Plasma concentration at the end of the dosing interval (GSK3640254 only)
Tmax	Time of maximum observed concentration (GSK3640254 and moxifloxacin)

NOTES:

- Additional parameters may be included as required.

7.2.2. Summary Measure

Pharmacokinetic parameters AUC(0-t), AUC(0-τ), Cmax, Cτ, and Tmax of GSK3640254 at steady state following repeat dose administration of GSK3640254 and PK parameters Cmax and Tmax of moxifloxacin following single dose administration of moxifloxacin on Day 7.

7.2.3. Population of Interest

The secondary PK analyses will be based on the PK concentration population for plasma PK concentrations, and the PK parameter population for plasma PK parameters, unless otherwise specified.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.2.1.2will be summarized using descriptive statistics and listed.

For Part 2, plasma PK parameters (AUC[0-t], AUC[0-τ], Cmax, Cτ, and Tmax) will be estimated for GSK3640254 and plasma PK parameters Cmax and Tmax will be estimated for moxifloxacin. Summary statistics (arithmetic mean, geometric mean, median, standard deviation (SD), coefficient of variation (CV), minimum, maximum, between-subject coefficient of variation (CVb), and 95% confidence interval (CI) for plasma GSK3640254 and moxifloxacin PK parameter values will be summarized by treatment.

- Additionally, pre-dose (trough) PK plasma concentrations of GSK3640254 will be summarized and used to assess achievement of steady state. Assessment of steady-state GSK3640254 concentrations will be assessed in Part 2 by estimating the slope of pre-dose concentrations. The final assessment of the slope will be determined by at least the last 3 pre-dose concentrations.

8. CARDIODYNAMIC ANALYSES (PART 2 ONLY)

8.1. Cardiodynamic ECG Endpoints

The primary endpoint is placebo-corrected change-from-baseline QTc (ΔΔQTc). In the absence of a substantial effect on HR, the Fridericia method (QTcF) will be used for HR correction and corresponding primary endpoint is ΔΔQTcF. If a substantial HR effect is observed (i.e., the largest least squares [LS] mean ΔΔHR is greater than 10 bpm in the by-time point analysis), other correction methods such as QTcS and QTcI will be explored and compared. The method that removes the HR dependence of the QT interval most efficiently will be chosen as the primary correction method.

The secondary endpoints are:

- Change-from-baseline HR, QTcF, PR, QRS intervals (ΔHR, ΔQTcF, ΔPR, and ΔQRS)
- If a substantial HR effect is observed: Change-from-baseline QTcS and QTcI (ΔQTcS, and ΔQTcI)
- Placebo-corrected ΔHR, ΔPR, and ΔQRS (ΔΔHR, ΔΔPR, and ΔΔQRS)
- If a substantial HR effect is observed: Placebo-corrected □QTcS, and/or □QTcI, and/or ΔQTcF (□□QTcS, □□QTcI, ΔΔQTcF) if not selected as the primary endpoint
- Categorical outliers for QTcF (and QTcS, and QTcI if a substantial HR effect is observed), HR, PR, and QRS
- Frequency of treatment-emergent changes for T-wave morphology and U-wave presence

8.2. Early Precision QT Analysis (EPQT)

Twelve-lead ECGs will be extracted in up to 10 replicates from each nominal time point prespecified in the protocol. The median value of each parameter from the set of evaluable beats in each extracted replicate will be calculated, and then the mean of all available medians (minimum 3 medians) from the nominal time point will be used as the subject's reportable value at that time point.

Early Precision QT analysis (formerly High Precision QT analysis) will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates (1 replicate consists of one 14 second ECG). Statistical quality control procedures will be used to review and assess all beats and identify "high" and "low" confidence beats using several criteria including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely)
- RR values exceeding or below certain thresholds (biologically unlikely)
- Rapid changes in QT, QTc, or RR from beat to beat

Placement of fiducials and measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates will be performed using the iCOMPAS software. All beats that are deemed "high confidence" will not be reviewed by an ERT cardiac safety

specialist. All low confidence beats will be reviewed manually by an ERT cardiac safety specialist and adjudicated using pass-fail criteria. The beats found acceptable by manual review will be included in the analysis. The beats confirmed to meet fail criteria will not be included in the analysis.

For the purpose of measuring PR and QRS intervals and to assess T-wave morphology and presence of U-waves, the TQT Plus algorithm will select the 3 ECG replicates with the highest quality score from the ECG extraction window. These 3 ECGs will be analyzed using a semi-automated process to determine these parameters. If 3 consecutive usable beats cannot be identified in at least 2 of the 3 replicates, then all beats in all replicates will be reviewed for that time point using a manual analysis.

If manual analysis is required, then all beats in a minimum of 3 replicates will be reviewed using the iCOMPAS software. The ERT cardiac safety specialist will review all usable beats in Lead II (or an alternate lead) for each replicate and will review and/or adjust the fiducial placements (onset of P, onset of Q, offset of S, and offset of T-wave that were electronically marked) of each waveform and also document the T-wave morphology and the presence of U-waves for each beat. A replicate will only be reported if it has 3 approved, usable beats.

8.3. General Methodology

All statistical analyses will be performed using the statistical software SAS for Windows Version 9.4 or higher (SAS Institute, Inc., Cary, NC). Data collected from all subjects enrolled in the study who receive at least 1 dose of study drug (GSK3640254, moxifloxacin, or placebo) will be presented in data listings. Both observed values and change-from-baseline values for each subject will be given where applicable. All continuous data will be listed with the same precision as will be presented in the database. Data listings will be sorted by subject ID, treatment, period, day, and time point and missing values will be represented by an empty cell.

For all descriptive statistics of continuous ECG parameters (i.e., HR, PR, QRS, and QTcF), data will be summarized including number of subjects (n), mean, median, standard deviation (SD), standard error (SE), 90% confidence interval (CI), minimum, and maximum by treatment and time point. For all modeling results of the by-time-point analysis of change-from-baseline values of continuous ECG parameters, n, least squares (LS) mean, SE, and 90% CI will be included. Modeling results of the by-time point analysis of placebo-corrected change-from-baseline will also include LS mean, SE, and 90% CI. Mean and median values will be rounded to the nearest tenth. SD, SE, and CI will be rounded to the nearest hundredth. For the concentration-QTc analysis, 2 decimal places will be shown for all effect estimates for all results which have an absolute value greater than 0.05. Each effect estimate with an absolute value ≤ 0.05 will be displayed with 2 significant figures. The CI of the effect estimate will display 1 more decimal place than the effect estimate. SE and *P* values will be reported with 4 digits and *P* values < 0.0001 will be reported as < 0.0001. Degrees of freedom (*df*), and t-value will be reported to the nearest tenth and nearest hundredth, respectively. Percentages will be rounded to the nearest tenths decimal place.

8.4. Baseline

For all continuous ECG parameters, baseline will be the average of the derived ECG intervals from the 3 ECG time points (−60, −45, and −30 minutes) prior to treatment administration on Day 1 within each respective period. For T-wave morphology and U-wave presence, baseline includes findings observed in any of the replicates from the 3 time points prior to dosing on Day 1 within each respective period.

8.5. QT Correction Methods

The QT and RR value for each beat will be used for HR correction. The primary HR correction method will be the Fridericia's correction (QTcF) defined as $QTcF\ (ms) = QT\ (ms)/[RR(ms)/1000]^{1/3}$.

If a substantial HR effect is observed (i.e., the largest least squares [LS] mean ΔΔHR is

greater than 10 bpm in the by-time point analysis), drug-free QT/RR data will be collected over a range of HR seen off-treatment on Day −1 to allow the generation of individualized QT correction methods. The QTc will be calculated from Day −1 of the first treatment period both during the periods of supine rest (QTcS) and from all evaluable QT/RR pairs in the 24-hour recording (QTcI). These data will be used to obtain the RR interval (HR) and QT data to enable derivation of QTcS and QTcI as follows.

- An individualized HR-corrected QT interval (QTcS) will be calculated from QT/RR data obtained at supine resting time points on Day −1 of the first treatment period. Based on QT/RR pairs from all subjects, the QTcS correction coefficient will be derived from a linear mixed-effects model: $\log(QTij) = \log(ai) + b1i \times \log(RRij) + b2i \times genderi + b3i \times \log(RRij) \times genderi + \varepsilon ij$ for i-th subject and j-th time point with gender included as a fixed effect for both intercept and slope, and subject included as a random effect for both intercept and slope. The coefficient of log(RR) for each subject, $bi = b1i + b3i \times genderi$, will then be used to calculate QTcS for each subject as follows: $QTcS = QT/RR^{bi}$.
- An optimized HR-corrected QT interval (QTcI) will be derived from a broader range of HRs by using all QT/RR data from the full 24-hour recording (all acceptable beats) on Day −1 of the first treatment period. The QT/RR pairs from each subject will be used for that subject's individual correction coefficient, which will be derived from a simple linear regression model: $\log(QTij) = \log(ai) + bi \times \log(RRij) + \varepsilon i$ for i-th subject and j-th time point. The coefficient of log(RR) for each subject, bi, will then be used to calculate QTcI for that subject as follows: $QTcI = QT/RR^{bi}$.

For QTcS and QTcI, the individual correction coefficients, b_i, will be listed and also summarized in a table using arithmetic mean, SE, number of subjects, and 90% CI (based on *t*-distribution).

The method that removes the HR dependence of the QT interval most efficiently will be chosen as primary correction method.

8.6. Evaluation of QT/RR correction methods

In case a substantial HR effect is observed, the relationship between QTc (QTcF and, if derived, QTcS [individual], and QTcI [optimized]) and RR interval will be investigated using on-treatment data (GSK3640254, moxifloxacin, and placebo) by a simple linear regression model: $QTc_{ij} = c_i + d_i \times RR_{ij} + \varepsilon_i$ for i-th subject and j-th time point. Mean QTc and RR values from all nominal post-baseline time points (including single pre-dose and post-dose time points on Day 7 in each period) will be used. The RR coefficient for each subject, d_i, will then be used to calculate the average sum of squared slopes (SSS) for each of the different QT/RR correction methods. The correction method that results in the average on-treatment slope closest to 0 (the smallest average SSS, as described by Tornøe, 2011) for GSK3640254 and placebo will be deemed the most appropriate HR correction method. If different methods show similar SSS values on placebo as on GSK3640254, priority in the choice will be given to the placebo results. In addition, a scatter plot and quantile plot of QTc (QTcF, QTcS, and QTcI) and RR intervals by treatment with regression line and a linear mixed-effects line (90% CI), respectively, will also be given. (The scatter plot and quantile plot of QTcF and RR intervals will be given if there is not a substantial HR effect).

8.7. Concentration-QTc Analysis (Primary Analysis)

The relationship between GSK3640254 plasma concentrations and ΔQTc (ΔQTcF or ΔQTc corrected with the method chosen as primary if a substantial HR effect is observed) will be quantified using a linear mixed-effects modelling approach. The model will have ΔQTc as the dependent variable, GSK3640254 plasma concentration as the exploratory variate (0 for placebo), centred baseline QTc (i.e., baseline QTc for individual participant minus the population mean baseline QTc for all participants in the same treatment period) as an additional covariate, treatment (active = 1 or placebo = 0) and time (i.e., post-baseline time point on Day 7 in each period, including pre-dose and post-dose time points on Day 7 in each period) as fixed effects, and random effects on intercept and slope per participant [Garnett, 2018]. In all calculations, concentrations in participants who received placebo will be set to zero. GSK3640254 plasma concentrations below the quantifiable limit at pre-dose on Day 7 in each period will be set to zero and after dosing on Day 7 in each period will be set to 1/2 the lower limit of quantitation in the concentration-QTc analysis.

An unstructured covariance matrix will be specified for the random effects. If convergence cannot be achieved even after appropriate rescaling of the concentrations, the random effect on the slope and intercept will be dropped, in this order, until convergence is achieved. The degrees of freedom of estimates will be determined by the Kenward-Roger method. From the model, the slope (i.e., the regression parameter for concentration) and the treatment effect-specific intercept (defined as the difference between active and placebo) will be estimated together with the 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

The geometric mean of the individual Cmax values for participants in each of the active dose groups will be determined. The predicted effect and its 2-sided 90% CI for ΔΔQTc (i.e., slope estimate × concentration + treatment effect-specific intercept) at this geometric mean Cmax of GSK3640254 will be obtained. If the upper bound of the 2-sided 90% CI of the predicted effect of ΔΔQTc at clinically relevant plasma levels of

GSK3640254 is below 10 ms, it will be concluded that GSK3640254 does not cause clinically relevant QTc prolongation within the observed plasma concentration range.

The plot of the observed median-quantile GSK3640254 concentrations and associated mean placebo-adjusted ΔQTc (i.e., ΔΔQTc) with 2-sided 90% CI adjusted for diurnal effects, together with the regression line presenting the predicted ΔΔQTc (2-sided 90% CI) [Tornøe, 2011] will be used to evaluate the adequacy of the model fit to the assumption of linearity and the impact on quantifying the C-QTc relationship. The observed ΔQTc values from the active group will be adjusted by the estimated time effect from the C-QTc model (i.e., the estimated diurnal effect under the placebo treatment). The individually estimated placebo-adjusted ΔQTci,j equals the individual ΔQTci,j for participant i administered GSK3640254 at time point j minus the estimation of time effect at time point j. Additional exploratory analyses (via graphical displays and/or model fitting) will include accounting for a delayed effect (hysteresis) and the justification for the choice of cardiodynamic model (linear versus nonlinear) as follows.

The SAS code for the concentration-QTc analysis is as follows:

```
PROC MIXED DATA=PKPD method=reml;
CLASS SUBJID TIME;
MODEL DQTC=TRT TIME CONC CBASE/ solution cl noint alpha=0.1 alphap=0.1 COVB DDFM=KR;
RANDOM INT CONC /type=UN SUBJECT=SUBJID s;
ESTIMATE 'Pred Mean Diff for T1' TRT 1 CONC &GeoMeanCmax_1 / CL ALPHA=0.1;
RUN;
```

Where PKPD=PK/QTc population, SUBJID=subject number, TRT=treatment (active=1 or placebo=0), TIME=nominal post-baseline time point, CONC=plasma concentration of GSK3640254, CBASE=centered baseline QTc, T1= active dose 1, GeoMeanCmax_1=geometric mean C_{max} for active dose 1, and DQTC=ΔQTc.

Note: the ESTIMATE statement will be repeated for other active dose groups.

8.7.1. Investigation of Hysteresis

Hysteresis will be assessed based on joint graphical displays of the LS mean difference between ΔQTc under GSK3640254 and under placebo (ΔΔQTc) for each post-baseline time point from the by-time point analysis and the mean concentrations of GSK3640254 at the same time points. In addition, hysteresis plots will be given for LS mean ΔΔQTc and the mean concentrations. If a QT effect (ΔΔQTc) >10 ms cannot be excluded in the by-time point analysis in the 2 active dose groups, and if the mean peak ΔΔQTc effect is observed at the same time point in the by-time point analysis in the 2 active dose groups, and if a delay between peak ΔΔQTc and peak plasma concentration in the plot (ΔΔQTc versus GSK3640254) of more than 1 hour is observed in a consistent way for the 2 active dose groups, other C-QTc models, such as a model with an effect compartment, may be explored. With the provision stated above, hysteresis will be assumed if the curve of the hysteresis plot shows a counterclockwise loop. A significant treatment effect-specific intercept is not biologically plausible and therefore may be indicative of hysteresis or model misspecification, if it cannot be explained by a nonlinear relationship.

8.7.2. Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal Q-Q plots for the standardized residuals and the random effects, and plots of standardized residuals versus concentration, fitted values of ΔQTc, centered baseline QTc, nominal time, and active treatment will be produced. Scatter plots for standard residuals versus continuous covariates and box plots for standard residuals versus discrete covariates will be provided. The scatter plots of standardized residuals versus concentration and versus centered baseline QTc by LOESS fitting (i.e., locally weighted scatter plot smoothing as described by [Cleveland, 1979]) will also be produced with optimal smoothing parameters selected by the Akaike information criterion with a correction (Hurvich, 1998). A scatter plot of observed concentration and ΔQTc with a LOESS smooth line with 90% CI and a linear regression line will also be provided to check the assumption of a linear C-QTc relationship. If there is an indication that a linear model is inappropriate, additional models may be fitted, in particular an Emax model. The C-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

8.8. Assay Sensitivity

The analysis to show assay sensitivity will be based on the concentration-QTc analysis of the effect on ΔQTc of 400 mg oral moxifloxacin using a similar model as for the primary analysis. That is, the relationship between moxifloxacin plasma concentration and ΔQTc will be investigated by linear mixed-effects modeling. The model will include ΔQTc as the dependent variable, moxifloxacin plasma concentration as the explanatory variable (0 for placebo), centred baseline QTc (i.e., baseline QTc for individual subject minus the population mean baseline QTc for all subjects in the same treatment period) as an additional covariate, treatment (moxifloxacin = 1 or placebo = 0) and time (i.e., post-dose time point on Day 7 in each period) as fixed effects, and random effects on intercept and slope per participant (Garnett, 2018). The geometric mean of the individual Cmax values for participants receiving the single dose of 400 mg moxifloxacin will be determined. The predicted effect and its 2-sided 90% CI for ΔΔQTc (i.e., slope estimate × concentration + treatment effect-specific intercept) at this geometric mean Cmax will be obtained.

If the slope of the moxifloxacin plasma concentration/ΔQTc relationship is statistically significant at the 10% level in a 2-sided test and the lower bound of the 2-sided 90% CI of the predicted QT effect at the observed geometric C_{max} of the 400 mg dose is above 5 ms, assay sensitivity will be deemed to have been demonstrated.

8.9. By-Time Point Analysis (Secondary Analysis)

The “by-time point analysis” for QTc (QTc or QTc corrected with the method chosen as primary if a substantial HR effect is observed) will be based on a linear mixed-effects model with ΔQTc as the dependent variable, period, sequence, time (i.e., post-baseline time point on Day 7 in each period: categorical), treatment (therapeutic dose of GSK3640254, supratherapeutic dose GSK3640254, moxifloxacin, and placebo), and time-by-treatment interaction as fixed effects, and baseline QTc as a covariate. An unstructured covariance matrix will be specified for the repeated measures at post-

baseline time points for participant within treatment period. If the model with an unstructured covariance matrix fails to converge, other covariance matrices such as autoregressive and compound symmetry will be considered. The model will also include a participant-specific random effect. If the fixed effects for period and/or sequence should prove to be not significant (that is, if the p-value >0.1), these effects may be removed from the model and the analysis will be repeated without those covariates. From this analysis, the LS mean, SE, and 2-sided 90% CI will be calculated for the contrast "GSK3640254 versus placebo" for each dose of GSK3640254 at each post-baseline time point, separately.

For HR, PR, QRS interval, and QTc with the methods not selected as primary the analysis will be based on the change-from-baseline post-dosing (ΔHR, ΔPR, ΔQRS, and ΔQTc). The same (by-time point analysis) model will be used as described for QTc. The LS mean, SE, and 2-sided 90% CI from the statistical modeling for both change-from-baseline and placebo-corrected change-from-baseline values will be listed in the tables and graphically displayed.

The SAS code for the by-time point analysis for QTc is as follows.

```
PROC MIXED DATA=ECG;
CLASS SUBJID TREAT TIME PERIOD SEQUENCE;
MODEL DQTc=BASE TREAT TIME TREAT*TIME PERIOD SEQUENCE/DDFM=KR;
RANDOM INTERCEPT / SUBJECT =SUBJID TYPE=UN;
REPEATED TIME / SUBJECT = PERIOD*SUBJID TYPE=UN;
LSMEANS TREAT*TIME/CL DIFF ALPHA=0.1;
RUN;
```

Where ECG = QT/QTc population, SUBJID = subject identifier, TREAT = treatment (therapeutic dose of GSK3640254, supratherapeutic dose of GSK3640254, moxifloxacin, and placebo), TIME = nominal post-baseline time point, BASE = baseline QTc, PERIOD = period, SEQUENCE= sequence, and DQTc = ΔQTc.

8.10. Categorical Analysis

Results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts and percentages for both number of subjects and number of time points. Subject data will be summarized using the count of distinct subjects that fall into the category and the percentage of the total number of subjects. Time point data will be summarized using the count of time points at which the assessments fall into the category and the percentage of the total number of time points at which assessments are performed. Counts (either number of subjects or number of time points) for each treatment group (therapeutic dose of GSK3640254, supratherapeutic dose GSK3640254, moxifloxacin, and placebo) will be used as the denominator in the calculation of percentages unless otherwise specified.

A subject or time point will be determined as an outlier if the following criteria (which are assessed separately) are met for the ECG intervals (Table 2).

Table 2 Criteria for determining a subject or time point outlier

ECG interval	Categorical outlier criteria
QTc (QTcF, QTcS, and QTcI)	Treatment-emergent value of > 450 and ≤ 480 ms when not present at baseline (new onset)
	Treatment-emergent value of > 480 and ≤ 500 ms when not present at baseline (new onset)
	Treatment-emergent value of > 500 ms when not present at baseline (new onset)
	Increase of QTc from baseline of > 30 and ≤ 60 ms
	Increase of QTc from baseline > 60 ms
PR	Increase of PR from baseline > 25% resulting in PR > 200 ms
QRS	Increase of QRS from baseline > 25% resulting in QRS > 120 ms
HR	Decrease of HR from baseline >25% resulting in HR < 50 bpm
	Increase of HR from baseline >25% resulting in HR > 100 bpm

All outliers will be summarized for each treatment group on the basis of incidence rates. A subject will be counted only once for a particular outlier event if the subject experiences more than 1 episode of that event. The total number of time points will be based on the number of observed time points across all subjects within a treatment group.

For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed, i.e., changes not present at baseline. For each category of T-wave morphology and of U-waves, the category will be deemed as present if observed in any replicates at the time point.

The T-wave morphology and U-wave presence categories are described as follows (Table 3).

Table 3 T-wave morphology and U-wave presence categories (assessed manually)

Category	Description
Normal T-wave (+)	Any positive T-wave not meeting any criterion below.
Flat T-wave	T-amplitude < 1 mm (either positive or negative), including flat isoelectric line.
Notched T-wave (+)	Presence of notch(es) of at least 0.05 mV amplitude on ascending or descending arm of the positive T-wave.
Biphasic	T-wave that contains a second component with an opposite phase that is at least 0.1 mV deep (both positive/negative and negative/positive and polyphasic T-waves included).
Normal T-wave (-)	T-amplitude that is negative, without biphasic T-wave or notches.
Notched T-wave (-)	Presence of notch(es) of at least 0.05 mV amplitude on descending or ascending arm of the negative T-wave.

Category	Description
U-waves	Presence of abnormal U-waves.

8.11. Terminology and Definitions: Placebo-corrected ΔQTc and Placebo-adjusted ΔQTc (ΔΔQTc)

Change-from-baseline QTc (ΔQTc) will be used as the dependent variable in the concentration-QTc analysis and in the by-time point analysis.

By-time point analysis

Placebo-corrected ΔQTc (ΔΔQTc)

- In the by-time point analysis on the QTc interval, LS mean, SE, and 2-sided 90% CI of ΔQTc and ΔΔQTc will be calculated for the active dose group and moxifloxacin group as well as on placebo group for ΔQTc at each post-baseline time point.

Concentration-QTc analysis

Placebo-corrected ΔQTc (ΔΔQTc)

- In the concentration-QTc analysis, the term placebo-corrected ΔQTc (ΔΔQTc) will be used for the model-predicted effect across concentrations on a population level.
    - *Definition*: Model-predicted mean ΔQTc in active dose group or moxifloxacin group minus model-predicted mean ΔQTc in the placebo group, which equals slope estimate × concentration + treatment effect-specific intercept.
- The term placebo-corrected ΔQTc (ΔΔQTc) will be used for the model-predicted effect on the QTc interval in the concentration-QTc prediction tables and the scatter plots for concentration-QTc model(s), quantile plots, and prediction plots, as described in Section 11.9.9.

Placebo-adjusted ΔQTc (ΔΔQTc)

- In the concentration-QTc analysis, the term placebo-adjusted ΔQTc (ΔΔQTc) will be used to illustrate the underlying data on both subject and population levels.
- *Definition for the estimated placebo-adjusted ΔQTc on a subject level:* observed ΔQTc for each subject (on active dose group or moxifloxacin group or placebo group) minus the estimated time effect (i.e., the model-predicted mean ΔQTc in the placebo group).
    - This term will be used to illustrate the underlying data on a subject level in the scatter plot(s) for concentration-QTc model(s).
- *Definition for the estimated placebo-adjusted ΔQTc term on a population level:* the average of individually estimated placebo-adjusted ΔQTc values at the associated median plasma concentration within each concentration decile.
    - This term will be used to illustrate the underlying data on a population level in the quantile plot(s).

9. SAFETY ANALYSES

The safety analyses will be based on the Safety population unless otherwise specified.

9.1. Adverse Events Analyses

Adverse events analyses including the analysis of AEs, SAEs, AEs of special interest, and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 9: List of Data Displays.

For studies with greater than one treatment period (e.g., crossover study), if AE onset is during one period and worsens during a later period, it would be counted in both periods. For the later period the onset date of AE with elevated grade would be the first dose date of the later treatment period.

9.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of chemistry laboratory tests, hematology laboratory tests, urinalysis, liver function tests, and pregnancy test will be based on GSK Core Data Standards and will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.1, July 2017). Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and gamma-glutamyl transferase will be summarized versus time. The details of the planned displays are in Appendix 9: List of Data Displays.

9.3. Adverse Events of Special Interest

At the end of the study, QT prolongation, gastrointestinal intolerability, gastric toxicity, psychiatric events, skin and subcutaneous tissue disorders and nervous system disorders will be summarized by treatment. A listing will also be provided accordingly.

QT prolongation AE of special interest will be defined as cardiac disorders system organ class (SOC) plus preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA) Standardized MedDRA Query (SMQ) “Torsade de pointes/QT Prolongation” (narrow and broad terms) plus seizure.

Gastrointestinal intolerability and gastric toxicity AEs of special interest will be defined within three narrow sub-SMQs [Gastrointestinal nonspecific symptoms and therapeutic procedures SMQ; Gastrointestinal nonspecific dysfunction SMQ; Gastrointestinal nonspecific inflammation (SMQ)] plus a selection of relevant broad PTs from the Gastrointestinal non-specific symptoms and therapeutic procedures SMQ.

Psychiatric AEs of special interest will be defined within the following:

- Sub-SMQ “Suicide/self-injury” (SMQ) from parent SMQ of “Depression and Suicide/Self Injury”. Only narrow terms from the sub-SMQ selected.

- Sub-SMQ “Depression (excluding suicide and self-injury)” (SMQ) from parent SMQ of “Depression and Suicide/Self Injury”. Only narrow terms from the sub-SMQ selected.
- All preferred terms from high level group term (HLGT) “Manic and Bipolar mood disorders and disturbances” under SOC “Psychiatric disorders”.
- Narrow terms from SMQ “Psychosis and psychotic disorders” selected.
- All preferred terms from HLGT “Anxiety disorders and symptoms”, under SOC “Psychiatric disorders”.
- All preferred terms from HLGT “Sleep Disorders and Disturbances” and HLGT “Sleep disturbances (incl subtypes)”.

Nervous system disorders AEs of special interest will be defined within the following:

- Four HLGTs under Nervous System Disorders SOC: “Headaches”; “Mental impairment disorders (excluding dementia)”; “Disturbance in consciousness” and “Seizures and seizure disorder”

Skin and subcutaneous tissue disorder AEs of special interest will be defined with the following PTs:

Dermatitis, Dermatitis allergic, Dermatitis atopic, Eczema, , Eczema nummular, , Skin irritation, Urticarial dermatitis, Eyelid pruritis, Pruritus, Pruritus allergic, Rash pruritic, Rash, Rash macular, Rash maculopapular, Rash morbilliform, Rash papular, Rash pruritic, Urticaria, Drug eruption and Rash pustular.

9.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs, vital signs, liver events, and Columbia Suicide Severity Rating Scale (C-SSRS) will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 9: List of Data Displays.

9.5. COVID 19 Related Analyses

Based on GSK’s “Impact of COVID-19 on Assessment of Safety in Clinical Trials Points to Consider”, it is GSK’s recommendation that study teams should capture COVID-19 cases based on the WHO criteria using the categories of: suspected, probable, and confirmed cases. COVID-19 eCRF pages are used in the study for data collection and analysis purposes. After a discussion with the study team, the following analyses will be included:

- Number of subjects with suspected, probable or confirmed for COVID-19 infection
- Number of subjects who had a COVID-19 diagnosis test performed and the number of subjects with positive, negative, or indeterminate results
- Incidence of COVID-19 as reported as an AE and SAE
- Incidence of treatment discontinuation due to AE of COVID-19 infection
- Severity, duration, and outcome of COVID-19 AEs

- If percentage of COVID-19 cases is >10% (>= 2 subjects for Part 1 and >=5 subjects with an AE of COVID-19), a summary of COVID-19 symptoms for subjects with COVID-19 AE will be added.

Further display details are provided in Appendix 9: List of Data Displays.

10. REFERENCES

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ViiV Healthcare group of companies Document Number 2019N422946_00 (10SEP2020) A Study to Evaluate the Effect of Therapeutic and Supratherapeutic Oral Doses of GSK3640254 on Cardiac Conduction as Assessed by 12-Lead Electrocardiogram Compared to Placebo and a Single Oral Dose of Moxifloxacin in Healthy Adult Participants

11. APPENDICES

11.1. Appendix 1: Schedule of Activities

11.1.1. Protocol Defined Schedule of Events

Screening Visit – Part 1

Procedure	Screening (up to 28 days before Day 1)
Informed consent	X
Inclusion and exclusion criteria	X
Demography	X
Full physical examination including height and weight[1]	X
Laboratory assessments (hematology, chemistry, urinalysis)	X
12-lead electrocardiogram	X
24-hour Holter monitor recording[2]	X
Vital sign measurements	X
Medication/drug/alcohol history	X
Past and current medical conditions	X
Columbia-Suicide Severity Rating Scale	X
Serum pregnancy test	X
Follicle-stimulating hormone (as needed, to confirm postmenopausal status)	X
Drug, alcohol, and cotinine screen	X
Human immunodeficiency virus, hepatitis B and C screening	X
Molecular test for SARS-CoV-2[3]	

1. A full physical examination will include at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.
2. May be performed either during Screening or on Day -2 upon admission.
3. Two consecutive approved molecular tests (polymerase chain reaction or antigen test). The first test should be performed ≥7 days prior to admission.

Time and Events Table – Part 1, Supratherapeutic Dose Selection

Procedure	Check-in	Baseline	Treatment							Follow-up		Notes
	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9[1]	
Admit to clinic	X											
Discharge from clinic											X	Discharge from clinic following completion of the last study procedure on Day 14.
Brief physical examination	X								X		X	An interim symptom-targeted brief physical examination will be performed at the discretion of the investigator. See Protocol Section 8.2.1 for a description of the brief physical examination.
Vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	Blood pressure and pulse will be measured in triplicate pre-dose on Day 1. Single blood pressure and pulse will be measured on other study days.
Daily temperature check	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X	X	X			X			X		X	The pre-dose ECG on Day 1 will be collected in triplicate. Other ECGs will be single. The ECGs on Days 1, 4, and 7 will be collected at pre-dose and post-dose at 2, 4, and 6 hours.
Drug, alcohol, and cotinine screen	X											See Protocol Appendix 2 for specific tests to be performed.
Molecular Test for SARS-CoV-2	X[1]							X			X	[1]This second test should be performed 24 hours prior to admission to the unit. Participants should be quarantined within the unit until the second test result is negative. Once the second test result is confirmed to be negative, they can be released into the unit and follow infection control practices.

Procedure	Check-in	Baseline	Treatment							Follow-up		Notes
	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9[1]	
Laboratory assessments (hematology, chemistry, urinalysis)	X				X				X		X	See Protocol Appendix 2 for specific tests to be performed.
Pregnancy test	X										X	Serum testing on Day -1.
Columbia-Suicide Severity Rating Scale	X			X		X		X		X		
Randomization			X									
Study intervention: Sentinel Cohort 1: GSK3640254 500 mg or placebo once daily Sentinel Cohort 2 (optional): To be determined after completion of Cohort 1 and not to exceed 500 mg BID			X	X	X	X	X	X	X			
GSK3640254 PK sampling			X				X	X	X	X	X	Blood collection for PK analysis of GSK3640254 will be collected within 40 minutes prior to the morning dose on Days 1, 5, 6, and 7, and after dosing on Day 7 at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 12, 24, and 48 hours.
AE review		←==========X==========→										
SAE review	←==========X==========→											
Concomitant medication review	←==========X==========→											

AE = adverse event; D = day; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event.

1. Evaluations scheduled for Day 9 will also be performed for participants who discontinue early.

Screening Visit – Part 2, Thorough QT Study

Procedure	Screening (up to 29 days before Day -2)
Informed consent	X
Inclusion and exclusion criteria	X
Demography	X
Full physical examination including height and weight[1]	X
Laboratory assessments (hematology, chemistry, urinalysis)	X
12-lead electrocardiogram	X
24-hour Holter monitor recording[2]	X
Vital sign measurements	X
Medication/drug/alcohol history	X
Past and current medical conditions	X
Columbia-Suicide Severity Rating Scale	X
Serum pregnancy test	X
Follicle-stimulating hormone (as needed, to confirm postmenopausal status)	X
Drug, alcohol, and cotinine screen	X
Human immunodeficiency virus, hepatitis B and C screening	X
Molecular test for SARS-CoV-2[3]	X

1. A full physical examination will include at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.
2. May be performed either during Screening or on Day -2 upon admission.
3. Two consecutive approved molecular tests (polymerase chain reaction or antigen test). The first test should be performed >= 7 days prior to admission.

Time and Events Table – Part 2, Thorough QT study

Procedure	Check -in	Baseline	Periods 1, 2, and 3							W	Period 4							Follow-up		Notes
	D -2	D -1	D1	D2	D3	D4	D5	D6	D7	D8-14[1]	D1	D2	D3	D4	D5	D6	D7	D8	D9[2]	
Admit to clinic	X																			
Discharge from clinic																			X	Final discharge from clinic following completion of the last study procedure on Day 9 of Period 4.
Brief physical examination	X									D14									X	An interim symptom-targeted brief physical examination will be performed at the discretion of the investigator. See Protocol Section 8.2.1 for description of the brief physical examination.
Vital signs	X	X	X	X	X	X	X	X	X	D8, D14	X	X	X	X	X	X	X	X	X	Blood pressure and pulse will be measured in triplicate pre-dose on Day 1 of each period and single blood pressure and pulse will be measured on other study days. On Day 7 of each period, blood pressure and pulse to be measured before dosing and 4 and 24 hours after dosing.
Daily temperature check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	While confined to clinic.
Safety 12-lead ECG	X	X	X	X		X	X		X	D8, D14	X	X		X	X		X	X	X	The pre-dose ECGs on Day 1 of each period will be collected in triplicate. All other ECGs will be single. On Days 1, 4, and 7, ECGs will be collected at pre-dose and post-dose at 1, 2, 3, 4, 6, and 24 hours.

Procedure	Check -in	Baseline	Periods 1, 2, and 3							W	Period 4							Follow-up		Notes
	D -2	D -1	D1	D2	D3	D4	D5	D6	D7	D8-14[1]	D1	D2	D3	D4	D5	D6	D7	D8	D9[2]	
Drug, alcohol, and cotinine screen	X																			See Protocol Appendix 2 for specific tests to be performed.
Laboratory assessments (hematology, chemistry, urinalysis)	X									D8, D14									X	See Protocol Appendix 2 for specific tests to be performed.
Molecular Test for SARS-CoV-2	X							X		D13						X			X	1The second test should be performed 24 hours prior to admission to the unit. Participants should be quarantined within the unit until the second test result is negative. Once the second test result is confirmed to be negative, they can be released into the unit and follow infection control practices. Test to be obtained every 7 days from Check-in (regardless of period or washout) while in-house.
Pregnancy test	X									D14									X	Serum testing on Day -2.
Columbia Suicide Severity Rating Scale	X									D8									X	
Randomization			X																	Period 1 only.

Procedure	Check-in	Baseline	Periods 1, 2, and 3							W	Period 4							Follow-up		Notes
	D -2	D -1	D1	D2	D3	D4	D5	D6	D7	D8-14[1]	D1	D2	D3	D4	D5	D6	D7	D8	D9[2]	
Study intervention: GSK3640254 therapeutic or supratherapeutic dose, placebo, or moxifloxacin			X	X	X	X	X	X	X		X	X	X	X	X	X	X			Moxifloxacin treatment consists of GSK3640254 placebo on Days 1 through 6 with moxifloxacin on Day 7 only.
Holter ECG recording[3]		X	X						X	D8	X						X	X		
GSK3640254 PK sampling			X				X	X	X	D8	X				X	X	X	X		Blood collection for PK analysis will be collected within 40 minutes prior to dosing on Days 1, 5, 6, and 7. Day 7 post-dose samples will be collected at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours.
Moxifloxacin PK sampling									X	D8							X	X		Blood collection for PK analysis of moxifloxacin will be collected within 40 minutes prior to the dose on Day 7. Day 7 post-dose samples will be collected at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours.
AE review			←==========X==========→																	
SAE review	←==========X==========→																			
Concomitant medication review	←==========X==========→																			

AE = adverse event; D = day; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event; W = washout.

1. Participants may be furloughed during the washout portion of the respective period following Day 8 procedures after discussion with and approval of the investigator. If participants are furloughed during the washout period, they should return to the clinic on Day 14 for scheduled assessments prior to initiating the next period.
2. Evaluations scheduled for Day 9 of Period 4 will also be performed for participants who discontinue early.
3. Holter ECG recordings:

- On Day -1 (Baseline), continuous ECG recordings (Holter) will be extracted at the following time points (relative to the time of planned dosing on the next day): pre-dose at -45, -30, and -15 minutes, and then after the time of planned dosing at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours.
- On Day 1 of each period, continuous ECG recordings (Holter) will be performed starting approximately 2 hours before dosing and digital 12-lead ECGs will be extracted in replicates at -45, -30, and -15 minutes prior to dosing.
- On Day 7 of each period, continuous ECG recordings (Holter) will be performed starting approximately 2 hours before dosing and digital 12-lead ECGs will be extracted in replicates at pre-dose (single time point), and then at 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 hours after dosing.
- The timing and number of planned study assessments, including safety, pharmacokinetic (PK), or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging PK data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the competent authorities and the ethics committee before implementation.

11.2. Appendix 2: Study Phases and Treatment Emergent Adverse Events

11.2.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to study treatment start date(/time) and stop date(/time).

11.2.1.1. Study Phases for Lab, Electrocardiograms, and Vital Signs

Assessments and events will be classified according to the time of occurrence relative to study treatment start date(/time) and stop date(/time).

Study Phase	Definition
Pre-Treatment	Date and Time ≤Study Treatment Start Date and Time
On-Treatment	Study Treatment Start Date and Time <Date and Time ≤Study Treatment Stop Date and Time + 5 days
Post-Treatment	Date and Time >Study Treatment Stop Date and Time + 5 days

11.2.1.2. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before Day 1
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 5: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

11.2.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date and time is on or after treatment start date and time & on or before treatment stop date and time + 5 days. • Study Treatment Start Date and Time ≤AE Start Date and Time ≤Study Treatment Stop Date and Time + 5 days. • If the AE onset date is completely missing, the AE is considered as treatment emergent.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Please refer to Appendix 5: Reporting Standards for Missing Data for handling of missing and partial dates for AEs. Use the rules in this table if the adverse event onset date is completely missing.

11.3. Appendix 3: Data Display Standards & Handling Conventions

11.3.1. Reporting Process

Software	
• The currently supported versions of SAS software (9.4) will be used.	
Reporting Area	
HARP Server	\\us1salx00259.corpnet2.com
HARP Compound	\gsk3640254\mid213053\final_01
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1). • For creation of ADaM datasets (ADC1/ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for all reporting efforts described in the RAP.	

11.3.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH or non-ICH listings.

Formats
• All data will be reported according to the actual treatment the participant received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be rounded to integer, unless otherwise specified. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.

Planned and Actual Time	

• Reporting for tables, figures, and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses, and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the participant's listings.
  • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures (mean figures only for PK concentrations), summaries, and statistical analyses (excluding statistical analyses of PK parameters).	

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables except for determining the worst-case values. • Unscheduled visits will not be included in figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

11.3.3. Reporting Standards for Pharmacokinetics

Pharmacokinetic Concentration Data	

Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.
	Refer to IDSL Statistical Principle 6.06.1.
	For continuous data:
	• NQs at the beginning of a participant profile (i.e. before the first incidence of a measurable concentration) are deemed to be zero as it is assumed that in this circumstance no drug is yet measurable in the blood.
	• For NQs at the end of the participant profile (i.e. after the last incidence of a measurable concentration);
	  • for individual plots and PK analyses these are dropped (set to missing) as they do not provide any useful information (and can erroneously indicate that absolutely no drug is present)
	  • for summary statistics, these are set to 0 (to avoid skewing of the summary statistics)
	• Individual NQs which fall between two measurable concentrations are set to missing (individual values of this nature are assumed to be an anomaly)
	If two or more NQ values occur in succession between measurable concentrations, the profile will be deemed to have terminated at the last measurable concentration prior to these NQs. For the purpose of individual participant plots, these NQs will be set to 0, and the subsequent measurable concentrations will be retained. For the derivation of pharmacokinetic parameters, these NQs and any subsequent measurable concentrations will be omitted (set to missing).
	Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.

Pharmacokinetic Parameter Data	
Descriptive Summary Statistics, Graphical Displays and Listings	N, n, arithmetic mean, 95% CI of arithmetic mean, geometric mean, 95% CI of geometric mean, SD, SD of log (ln) data, CV (%), and between-subject geometric coefficient of variation (CVb (%)) will be reported. CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD[ln] = SD of Ln-Transformed data)
Parameters Not Being Ln-Transformed	Tmax, λz, λz lower, λz upper, and λz no. of points.
Parameters Not Being Summarized	λz, λz lower, λz upper, and λz no. of points.
Listings	Include the first point, last point and number of points used in the determination of λz and Rsq_adjusted for listings.

11.4. Appendix 4: Derived and Transformed Data

11.4.1. General

Multiple Measurements at One Analysis Time Point

- Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented.
- The worst finding/interpretation associated with multiple measurements as the finding/interpretation for that time point.
- Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.

Study Day

- Calculated as the number of days from Dose Date on Day 1:
  - Assessment Date = Missing
    → Study Day = Missing
  - Assessment Date <Dose Date on Day 1
    → Study Day = Assessment Date –Dose Date on Day 1
  - Assessment Date >= Dose Date on Day 1
    → Study Day = Assessment Date – Dose Date on Day 1 + 1

Period Day

- Calculated as the number of days from First Dose Date for the respective period:
  - Assessment Date = Missing
    → Period Day = Missing
  - Assessment Date <Dose Date on Day 1
    → Period Day = Assessment Date – Dose Date on Day 1 of that period
  - Assessment Date >= Dose Date on Day 1 on that period (including washout period)
    → Period Day = Assessment Date – Dose Date on Day 1 of that period + 1

11.4.2. Study Population

Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: o Any participant with a missing day will have this imputed as day '15'. o Any participant with a missing day and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height $(m)^2$]

11.4.3. Safety

Adverse Events
AEs of Special Interest
• QT prolongation • Gastrointestinal intolerability and gastric toxicity • Psychiatric events • Nervous system disorders • Skin and subcutaneous tissue disorders

11.5. Appendix 5: Reporting Standards for Missing Data

11.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (i.e., as specified in the protocol) was defined as the participant had completed all phases of the study including the final date on which data were or are expected to be collected. • Withdrawn participants will not be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

11.5.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be

Element	Reporting Detail
	missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.5.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 2: Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications	○ Partial dates for any concomitant medications recorded in the eCRF will be imputed using the following convention: ○ If the partial date is a start date, a ”01” will be used for the day and “Jan” will be used for the month ○ If the partial date is a stop date, a “28/29/30/31” will be used for the day (dependent on the month and year) and ”Dec” will be used for the month. ○ The recorded partial date will be displayed in listings.

11.6. Appendix 6: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

11.6.1. Laboratory Values

Laboratory abnormalities will be graded according to the DAIDS grading table Version 2.1, July 2017. Laboratory results are converted to use SI units; only the numeric part of the criteria will be used. If for a laboratory parameter there are multiple grades sharing the same criteria, the maximum grade will be used.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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11.7. Appendix 7: Values of Potential Clinical Importance

11.7.1. ECG

ECG Parameter	Units	Potential Clinically Important Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		>450
Absolute PR Interval	msec	<110	>200
Absolute QRS Interval	msec	<75	>110
Change from Baseline			
Increase from Baseline QTc	msec		>60

11.7.2. Vital Signs

Vital Sign Parameter (Absolute)	Units	Potential Clinically Important Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	<85	>140
Diastolic Blood Pressure	mmHg	<45	>90
Heart Rate	bpm	<40	>100

11.8. Appendix 8: Abbreviations & Trade Marks

11.8.1. Abbreviations

Abbreviation	Description
ΔHR	change from baseline in heart rate
ΔPR	change from baseline in PR interval
ΔQRS	change from baseline in QRS interval
ΔQTcF	change from baseline in QT interval corrected for heart rate using Fridericia's formula
ΔQTcI	change from baseline in optimized HR-corrected QT interval
ΔQTcS	change from baseline in individualized HR-corrected QT interval
ΔΔHR	placebo-corrected change from baseline in heart rate
ΔΔPR	placebo-corrected change from baseline in PR interval
ΔΔQRS	placebo-corrected change from baseline in QRS interval
ΔΔQTcF	placebo-corrected change from baseline in QT interval corrected for heart rate using Fridericia's formula
ΔΔQTcI	placebo-corrected change from baseline in optimized HR-corrected QT interval
ΔΔQTcS	placebo-corrected change from baseline in individualized HR-corrected QT interval
ADaM	analysis data model
AE	adverse event
ALT	alanine aminotransferase
AUC	area under the plasma concentration-time curve
AUC(0-τ)	AUC from time 0 to the end of the dosing interval at steady state
AUC(0-t)	Area under the plasma concentration-time curve from time zero to time t
BID	Twice daily
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
Cmax	maximum observed concentration
C-SSRS	Columbia suicide severity rating scale
C_τ	plasma concentration at the end of the dosing interval
CV_b	coefficient of variation (between)
C-QTc	concentration-corrected QT interval
DAIDS	division of AIDS
DBF	database freeze
DBR	database release
DP	decimal places
ECG	electrocardiogram
EPQT	Early Precision QT analysis technique (formerly Expert Precision QT)
eCRF	electronic case record form
GSK	GlaxoSmithKline
HIV	human immunodeficiency virus
HR	Heart rate
ICH	international conference on harmonization
IDSL	integrated data standards library

Abbreviation	Description
LLN	lower limit of normal
LOESS	Locally weighted scatter plot smoothing
LS	Least squares
NQ	not quantifiable
PK	pharmacokinetic
PR	PR interval of the ECG
QD	once daily
Q-Q	Quantile-quantile
QRS	QRS interval of the ECG
QT	QT interval of the ECG
QTc	corrected QT interval
QTcF	corrected QT interval using the Fridericia formula
QTcI	Optimized HR-corrected QT interval
QTcS	individualized HR-corrected QT interval
RAP	reporting & analysis plan
RR	RR interval of the ECG
SAC	statistical analysis complete
SAE	serious adverse event
SD	standard deviation
SDTM	study data tabulation model
SE	Standard error
SSS	Sum of squared slopes
Tmax	time of maximum observed concentration
TQT	Thorough QT
ULN	upper limit of normal

11.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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11.9. Appendix 9: List of Data Displays

11.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.8	
Safety	2.1 to 2.30	2.1 to 2.1
Pharmacokinetic	3.1 to 3.11	3.1 to 3.13
Cardiodynamic	4.1 to 4.10.2	4.1 to 4.19.2
Section	**Listings**	
ICH Listings	1 to 32	
Non-ICH Listings	33 to 43	

11.9.2. Mock Example Shell Referencing

Non-IDSL specifications will be referenced as indicated and if required example mock-up displays provided in the Table/Listing/Figure Shells.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Cardiodynamic	CD_Fn	CD_Tn	CD_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

11.9.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

11.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Randomized	NS1	Summary of Number of Subjects Enrolled by Country and Site ID		SAC
1.2.	Screened	SP1	Summary of Study Population		SAC
1.3.	Safety	ES1	Summary of Subject Disposition for the Subject Conclusion Record		SAC
1.4.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failures		SAC
Protocol Deviation					
1.5.	Safety	DV1	Summary of Important Protocol Deviations		SAC
Demographic and Baseline Characteristics					
1.6.	Safety	DM1	Summary of Demographic Characteristics		SAC
1.7.	Safety	DM5	Summary of Race and Racial Combinations		SAC
1.8.	Safety	DM11	Summary of Age Ranges		SAC

11.9.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
2.1.	Safety	AE1CP	Summary of Adverse Events by System Organ Class and Preferred Term		SAC
2.2.	Safety	AE1CP	Summary of Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
2.3.	Safety	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency		SAC
2.4.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
2.5.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
2.6.	Safety	AE5A	Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Intensity		SAC
2.7.	Safety	AE1CP	Summary of Adverse Events of Special Interest		SAC
Laboratory: Chemistry					
2.8.	Safety	LB1	Summary of Clinical Chemistry Changes from Baseline		SAC
2.9.	Safety	LB1	Summary of Clinical Chemistry Values		SAC
2.10.	Safety	LB16	Summary of Clinical Chemistry Results by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC
Laboratory: Hematology					
2.11.	Safety	LB1	Summary of Hematology Changes from Baseline		SAC
2.12.	Safety	LB1	Summary of Hematology Values		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13.	Safety	LB16	Summary of Hematology Results by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC
Laboratory: Urinalysis					
2.14.	Safety	UR3	Summary of Urinalysis Dipstick Results		SAC
2.15.	Safety	LB1	Summary of Urine Concentration Changes from Baseline		SAC
2.16.	Safety	LB1	Summary of Urine Concentration Values		SAC
2.17.	Safety	LB16	Summary of Urinalysis by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC
ECG					
2.18.	Safety	SAFE_T1	Summary of ECG Findings		SAC
2.19.	Safety	EG2	Summary of ECG Changes from Baseline		SAC
2.20.	Safety	EG2	Summary of ECG Values		SAC
2.21.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		SAC
2.22.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		SAC
Vital Signs					
2.23.	Safety	VS1	Summary of Vital Sign Changes from Baseline		SAC
2.24.	Safety	VS1	Summary of Vital Sign Values		SAC
C-SSRS					
2.25.	Safety	CSSRS4	Listing of C-SSRS Suicidal Ideation and Behavior Data	Only include participants who have suicidal ideation or behavior	SAC
Liver Event					

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.26.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC
2.27.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		SAC
COVID-19 Related AE					
2.28.	Safety	PAN1	Summary of COVID-19 Assessment		SAC
2.29	Safety	SAFE_T2	Summary of COVID-19 Adverse Event		SAC
2.30	Safety	PAN3	Summary of COVID-19 Symptoms for Subjects with Adverse Events	Conditional Display	SAC

11.9.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
3.1.	PK Concentration	PKCT1	Summary of GSK3640254 Plasma Pharmacokinetic Concentration-Time Data (ng/mL) by Treatment – Part 1	Part 1	SAC
3.2.	PK Concentration	PKCT1	Summary of Pre-dose (trough) GSK3640254 Plasma Pharmacokinetic Concentration-Time Data (ng/mL) by Treatment - Part 1	Part 1	SAC
3.3.	PK Concentration	PKCT1	Summary of GSK3640254 Plasma Pharmacokinetic Concentration-Time Data (ng/mL) by Treatment – Part 2	Part 2	SAC
3.4.	PK Concentration	PKCT1	Summary of Pre-dose (trough) GSK3640254 Plasma Pharmacokinetic Concentration-Time Data (ng/mL) by Treatment - Part 2	Part 2	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.5.	PK Concentration	PKCT1	Summary of Moxifloxacin Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment – Part 2	Part 2	SAC
PK Derived Parameters					
3.6.	PK Parameter	PKPT4	Summary Statistics of Derived GSK3640254 Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment – Part 1	Part 1 Parameters with units	SAC
3.7.	PK Parameter	PKPT4	Summary Statistics of Derived GSK3640254 Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment – Part 1	Part 1 Parameters with units	SAC
3.8.	PK Parameter	PKPT4	Summary Statistics of Derived GSK3640254 Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment – Part 2	Part 2 Parameters with units	SAC
3.9.	PK Parameter	PKPT4	Summary Statistics of Derived GSK3640254 Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment – Part 2	Part 2 Parameters with units	SAC
3.10.	PK Parameter	PKPT6	Summary Statistics of Derived Moxifloxacin Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment - Part 2	Part 2 Parameters with units	SAC
3.11.	PK Parameter	PKPT4	Statistical Analysis of Plasma GSK3640254 Pharmacokinetic Parameters Assessing Steady-State - Part 2	Part 2 Parameters with units	SAC

11.9.7. Cardiodynamic Tables (Part 2)

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
QT Correction Method					
4.1	QT/QTc population		QTcS, and QTcI individual correction coefficients with descriptive statistics	Number of subjects (n), mean, SD, SE, 90% CI, median, minimum, and maximum will be given	SAC
4.2	QT/QTc population		Average SSS for different QT-RR correction methods	SSS for GSK3640254, moxifloxacin, and placebo will be given	SAC
By-Time Point ECG Analysis					
4.3	QT/QTc population		Baseline values of ECG parameters with descriptive statistics	n, mean, SD, SE, 90% CI, median, minimum, and maximum from descriptive analysis will be given by treatment for each ECG parameter	SAC
4.4	QT/QTc population		Observed values of QTc (primary correction method) with descriptive statistics	n, mean, SD, SE, 90% CI, median, minimum, and maximum from descriptive statistics will be given by treatment and post-dose time point	SAC
4.5.1-4.5.6	QT/QTc population		Change-from-baseline QTcF, HR, PR, and QRS (and QTcS and QTcI if calculated) (ΔQTcF, ΔHR, ΔPR, ΔQRS, ΔQTcS, and ΔQTcI) at each time point	n, LS mean, SE, and 90% CI from the statistical modeling will be given by treatment and time point	SAC
4.6.1-4.6.6	QT/QTc population		Placebo-corrected change-from-baseline QTcF, HR, PR, and QRS (and QTcS and QTcI if calculated) (ΔΔQTcF, ΔΔHR, ΔΔPR, ΔΔQRS, ΔΔQTcS, and ΔΔQTcI) at each time point	LS mean, SE, and 90% CI from the statistical modeling will be given by treatment and time point	SAC
Categorical ECG Analysis					

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.7	QT/QTc population		Categorical analyses for QTc, HR, PR, and QRS	Number (%) of subjects and time points with QTc > 450 and ⩽ 480 ms, > 480 and ⩽ 500 ms, or > 500 ms by treatment; ΔQTc > 30 and ⩽ 60 ms, or > 60 ms by treatment; ΔPR > 25% and PR > 200 ms at post-dose; ΔQRS > 25% and QRS > 120 ms at post-dose; HR decrease from baseline > 25% and HR < 50 bpm at post-dose; and HR increase from baseline > 25% and HR > 100 bpm at post-dose	SAC
4.8	QT/QTc population		T-wave morphology and U-wave presence across treatments: treatment-emergent changes	Number (%) of subjects and time points falling into each of the T-wave categories: Normal (+), Flat, Notched (+), Biphasic, Normal (-), Notched (-) as well as U-wave category	SAC
Concentration-QTc Analysis					
4.9.1	PK/QTc population		Concentration-QTc analysis of GSK3640254 and associated ΔQTc prolongation	Fixed-effect estimations and corresponding P values will be given	SAC
4.9.2	PK/QTc population		Assay sensitivity analysis of moxifloxacin and associated ΔQTc prolongation	Fixed-effect estimations and corresponding P values will be given	SAC
4.10.1	PK/QTc population		Predicted ΔΔQTc interval at geometric mean peak GSK3640254 concentration for each model		SAC
4.10.2	PK/QTc population		Predicted ΔΔQTc interval at geometric mean peak moxifloxacin concentration		SAC

11.9.8. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
3.1.	PK Concentration	PKCF1P	Individual GSK3640254 Plasma Concentration-Time Plots by Participant – Part 1 (Linear and Semi-Logarithmic)	Part 1, Paginate by Participant Dashed line represents the LLQ Treatments Overlaid	SAC
3.2.	PK Concentration	PKCF1P	Individual GSK3640254 Plasma Concentration-Time Plots by Participant – Part 2 (Linear and Semi-Logarithmic)	Part 2, Paginate by Participant Dashed line represents the LLQ Treatments Overlaid	SAC
3.3.	PK Concentration	PKCF1P	Individual Moxifloxacin Plasma Concentration-Time Plots by Participant – Part 2 (Linear and Semi-Logarithmic)	Part 2, Paginate by Participant Dashed line represents the LLQ Treatments Overlaid	SAC
3.4.	PK Concentration	PKCF1P	Individual GSK3640254 Plasma Concentration-Time Plots by Treatment – Part 1 (Linear and Semi-Logarithmic)	Part 1 Paginate by Treatment Dashed line represents the LLQ Individuals Overlaid	SAC
3.5.	PK Concentration	PKCF1P	Individual GSK3640254 Plasma Concentration-Time Plots by Treatment – Part 2 (Linear and Semi-Logarithmic)	Part 2 Paginate by Treatment Dashed line represents the LLQ Individuals Overlaid	SAC
3.6.	PK Concentration	PKCF1P	Individual Moxifloxacin Plasma Concentration-Time Plots by Participant – Part 2 (Linear and Semi-Logarithmic)	Part 2 Spaghetti Plot Dashed line represents the LLQ Individuals Overlaid	SAC
Mean / Median Concentration Plots					
3.7.	PK Concentration	PKCF2	Mean (Standard Deviation) GSK3640254 Plasma Concentration-Time Plots by Treatment – Part 1 (Linear and Semi-Logarithmic)	Treatments (A and B) Overlaid	SAC
3.8.	PK Concentration	PKCF3	Median (Range) GSK3640254 Plasma Concentration-Time Plots by Treatment – Part 1 (Linear and Semi-Logarithmic)	Treatments (A and B) Overlaid	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.9.	PK Concentration	PKCF2	Mean (Standard Deviation) Pre-dose (Trough) GSK3640254 Plasma Concentration Plots by Treatment – Part 1 (Linear and Semi-Logarithmic)	Treatments (A and B) Overlaid	SAC
3.10.	PK Concentration	PKCF2	Mean (Standard Deviation) GSK3640254 Plasma Concentration-Time Plots by Treatment – Part 2 (Linear and Semi-Logarithmic)	Treatments (T and ST) Overlaid	SAC
3.11.	PK Concentration	PKCF3	Median (Range) GSK3640254 Plasma Concentration-Time Plots by Treatment – Part 2 (Linear and Semi-Logarithmic)	Treatments (T and ST) Overlaid	SAC
3.12.	PK Concentration	PKCF2	Mean (Standard Deviation) Pre-dose (Trough) GSK3640254 Plasma Concentration Plots by Treatment – Part 2 (Linear and Semi-Logarithmic)	Treatments (T and ST) Overlaid	SAC
3.13.	PK Concentration	PKCF2	Mean (Standard Deviation) Moxifloxacin Plasma Concentration-Time Plots – Part 2 (Linear and Semi-Logarithmic)		SAC

11.9.9. Chardiodynamic Figures (Part 2)

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
QT Correction Method					
4.1	QT/QTc population		Scatter plots of QTc and RR by treatment	Scatter plots of QTc (QTcF, QTcS, and QTcI) and RR intervals by treatment with regression lines will be given	SAC
4.2	QT/QTc population		QTc-RR quantile plot by treatment	QTc-RR quantile plots (with quantiles) with linear mixed-effects line and 90% CI will be given	SAC
By-Time Point ECG Analysis					

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.3.1-4.3.6	QT/QTc population		Observed QTc (primary correction method) across time points	Mean and 90% CI from descriptive analysis will be given by treatment	SAC
4.4.1-4.4.6	QT/QTc population		Change-from-baseline QTcF, HR, PR, and QRS (and QTcS and QTcI if calculated) (ΔQTcF, ΔHR, ΔPR, ΔQRS, ΔQTcS, and ΔQTcI) across time point	LS mean and 90% CI from the statistical modeling will be shown by treatment	SAC
4.5	QT/QTc population		Placebo-corrected change-from-baseline QTcF, HR, PR, and QRS (and QTcS and QTcI if calculated) (ΔΔQTcF, ΔΔHR, ΔΔPR, ΔΔQRS, ΔΔQTcS, and ΔΔQTcI) across time point	LS mean and 90% CI from the statistical modeling will be shown by treatment	SAC
Concentration-QTc Analysis					
4.6.1	PK/QTc population		Mean GSK3640254 plasma concentrations over time		SAC
4.6.2	PK/QTc population		Mean moxifloxacin plasma concentration over time		SAC
4.7.1-4.7.2	PK/QTc population		Joint plot of GSK3640254 plasma concentrations and ΔΔQTc over time		SAC
4.8.1-4.8.2	PK/QTc population		Hysteresis plot of GSK3640254 plasma concentration and ΔΔQTc connected in temporal order		SAC
4.9.1	PK/QTc population		Scatter plot of observed GSK3640254 plasma concentrations and ΔQTc with simple linear regression line and LOESS regression	Scatter plot of ΔQTc versus concentration with LOESS line and 90% CI and simple regression line	SAC
4.9.2	PK/QTc population		Scatter plot of observed moxifloxacin plasma concentrations and ΔQTc with simple linear regression line and LOESS regression	Scatter plot of ΔQTc versus concentration with LOESS line and 90% CI and simple regression line	SAC
4.10.1	PK/QTc population		Scatter plot of observed GSK3640254 plasma concentrations and estimated placebo-corrected ΔQTc	Scatter plot of placebo-corrected ΔQTc versus concentration with linear mixed-effects regression line and 90% CI	SAC

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.10.2	PK/QTc population		Scatter plot of observed plasma concentrations of moxifloxacin and estimated placebo-corrected ΔQTc	Scatter plot of placebo-corrected ΔQTc versus concentration with linear mixed-effects regression line and 90% CI	SAC
4.11.1	PK/QTc population		Model-predicted ΔΔQTc (mean and 90% CI) and estimated placebo-corrected ΔQTc (mean and 90% CI) across deciles of GSK3640254 plasma concentrations		SAC
4.11.2	PK/QTc population		Model-predicted ΔΔQTc (mean and 90% CI) and estimated placebo-corrected ΔQTc (mean and 90% CI) across deciles of moxifloxacin plasma concentrations		SAC
4.12.1	PK/QTc population		Model-predicted ΔΔQTc interval (mean and 90% CI) at geometric mean peak GSK3640254 concentrations		SAC
4.12.2	PK/QTc population		Model-predicted ΔΔQTc interval (mean and 90% CI) at geometric mean peak moxifloxacin concentrations		SAC
4.13.1	PK/QTc population		Scatter plot of standardized residuals versus fitted values for GSK3640254		SAC
4.13.2	PK/QTc population		Scatter plot of standardized residuals versus fitted values for moxifloxacin		SAC
4.14.1	PK/QTc population		Scatter plot of standardized residuals versus concentrations with LOESS for GSK3640254		SAC
4.14.2	PK/QTc population		Scatter plot of standardized residuals versus concentrations with LOESS for moxifloxacin		SAC
4.15.1	PK/QTc population		Scatter plot of standardized residuals versus centered baseline QTc with LOESS for GSK3640254		SAC
4.15.2	PK/QTc population		Scatter plot of standardized residuals versus centered baseline QTc with LOESS for moxifloxacin		SAC
4.16.1	PK/QTc population		Box plot of standardized residuals versus nominal time for GSK3640254		SAC

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.16.2	PK/QTc population		Box plot of standardized residuals versus nominal time for moxifloxacin		SAC
4.17.1	PK/QTc population		Box plot of standardized residuals versus treatment for GSK3640254		SAC
4.17.2	PK/QTc population		Box plot of standardized residuals versus treatment for moxifloxacin		SAC
4.18.1	PK/QTc population		Normal Q-Q plot of standardized residuals for GSK3640254		SAC
4.18.2	PK/QTc population		Normal Q-Q plot of standardized residuals for moxifloxacin		SAC
4.19.1	PK/QTc population		Normal Q-Q plots of the estimated random effects for GSK3640254		SAC
4.19.2	PK/QTc population		Normal Q-Q plots of the estimated random effects for moxifloxacin		SAC

11.9.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Safety	ES3	Listing of Reasons for Study Withdrawal		SAC
2.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC
3.	Screened	ES7	Listing of Reasons for Screen Failure		SAC
Protocol Deviations					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.	Safety	DV2	Listing of Important Protocol Deviations		SAC
5.	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analyzed					
6.	Safety	SP3A	Listing of Subjects Excluded from Any Population		SAC
Demographic and Baseline Characteristics					
7.	Safety	DM2	Listing of Demographic Characteristics		SAC
8.	Safety	DM9	Listing of Race		SAC
Prior and Concomitant Medications					
9.	Safety	CM5	Listing of Concomitant Medications	Based on GSK Drug Dictionary	SAC
Exposure and Treatment Compliance					
10.	Safety	EX4	Listing of Exposure Data		SAC
11.	Safety	POP_L1	Listing of Meal Data		SAC
Adverse Events					
12.	Safety	AE2	Listing of Relationship Between System Organ Class and Verbatim Text		SAC
13.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
14.	Safety	AE9CP	Listing of All Adverse Events		SAC
15.	Safety	AE9CP	Listing of Adverse Events of Special Interest		SAC
Serious and Other Significant Adverse Events					
16.	Safety	AE9CP	Listing of Study Drug Related Adverse Events		SAC
17.	Safety	AE9CP	Listing of Serious Adverse Events (Fatal & Non-Fatal)		SAC
18.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
19.	Safety	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study		SAC
Hepatobiliary (Liver)					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
20.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC
21.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events		SAC
All Laboratory					
22.	Safety	LB5A	Listing of Clinical Chemistry with any Toxicities		SAC
23.	Safety	LB5A	Listing of All Clinical Chemistry Data for Subjects with any Toxicities		SAC
24.	Safety	LB5A	Listing of Hematology with any Toxicities		SAC
25.	Safety	LB5A	Listing of All Hematology Data for Subjects with any Toxicities		SAC
26.	Safety	LB5A	Listing of Urinalysis with any Toxicities		SAC
27.	Safety	LB5A	Listing of All Urinalysis Data for Subjects with any Toxicities		SAC
ECG					
28.	Safety	EG6	Listing of All ECG Findings		SAC
29.	Safety	EG6	Listing of All Abnormal ECG Findings		SAC
30.	Safety	EG4	Listing of All ECG Values		SAC
Vital Signs					
31.	Safety	VS5	Listing of All Vital Signs of Potential Clinical Importance		SAC
32.	Safety	VS5	Listing of All Vital Signs for Subjects with any Value of Potential Clinical Importance		SAC

11.9.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetics					
33.	PK Concentration	PKCL1P	Listing of GSK3640254 Plasma Concentration-Time Data by Treatment – Part 1	Part 1	SAC
34.	PK Concentration	PKCL1P	Listing of GSK3640254 Plasma Concentration-Time Data by Treatment – Part 2	Part 2	SAC
35.	PK Concentration	PKCL1P	Listing of Moxifloxacin Plasma Concentration-Time Data – Part 2	Part 2	SAC
36.	PK Parameter	PKPL1P	Listing of GSK3640254 Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment – Part 1	Part 1	SAC
37.	PK Parameter	PKPL1P	Listing of GSK3640254 Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment – Part 2	Part 2	SAC
38.	PK Parameter	PKPL1P	Listing of Moxifloxacin Plasma Pharmacokinetic Parameters Based on Actual Time - Part 2	Part 2	SAC
Cardiodynamic ECG Analysis					
39.1-6	QT/QTc Population		QTcF (and QTcI and QTcS intervals if calculated), HR, PR, and QRS intervals - observed and change-from-baseline values as well as categorical outliers	Part 2	SAC
40.	QT/QTc Population		T-wave morphology and U-wave presence		SAC
41.	PK/QTc Population		ΔQTc and time-matched GSK3640254 and moxifloxacin concentrations for each subject	Data for concentration-QTc analysis and assay sensitivity (Part 2)	SAC
COVID-19 Related AE					
42.	Safety	PAN12	Listing of COVID-19 Assessments and Symptom Assessment		SAC
43.	Safety	AE9CP	Listing of Adverse Events of COVID-19		SAC