Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for The Effect of Coadministration of GSK3640254 on the Pharmacokinetics of a Combined Oral Contraceptive Containing Ethinyl Estradiol and Levonorgestrel in Healthy Female Subjects
Compound Number	:	GSK3640254
Effective Date	:	19-JAN-2020

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 208135.
- 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.

RAP Team Approvals:

Approver	Date	Approval Method
PPD Principal Statistician, GSK Biostatistics	17-JAN-2020	Wet Ink Signature Page
PPD Programmer/Analyst, GSK Biostatics	17-JAN-2020	Wet Ink Signature Page
PPD Statistics Leader, GSK Biostatistics	17-JAN-2020	Wet Ink Signature Page
PPD Programming Director, GSK Biostatistics	19-JAN-2020	Wet Ink Signature Page

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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: 208135

1.1. RAP Amendments

Revision chronology:

RAP Section	Amendment Details
Reporting and Analysis Plan_Study208135_Final_V1 [16-JUL-2019]	
Reporting and Analysis Plan_Study208135_Amendment_Final_V1 [19-JAN-2020]	
7.1.4 and 7.2.4	• Add boxplots for pharmacokinetic (PK) parameters overlaid with subjects categorized by elevated alanine aminotransferase (ALT) level and categorized by progesterone level
9.1	• Add adverse events of special interests
9.2	• Add plots of ALT, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and gamma-glutamyl transferase by time
9.3	• Add liver events
11.4.3	• Add adverse events of special interest
11.9.4	• Add additional summary of treatment status and reasons for discontinuation from treatment
11.9.5	• Add summary of adverse events of special interests • Add summaries of actual values for clinical chemistry, hematology, urine concentration, electrocardiograms (ECGs), and vital signs • Add summaries for liver events
11.9.6	• Add figures of ALT, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and gamma-glutamyl transferase by time
11.9.8	• Add boxplots of ethinyl estradiol (EE), levonorgestrel (LNG), and GSK3640254 PK parameters against ALT • Add boxplots of EE, LNG, and GSK3640254 PK parameters against progesterone
11.9.11	• Add listings of adverse events of special interests, vital results for subjects with liver stopping events, and subjects with liver monitoring/stopping event reporting

2. SUMMARY OF KEY PROTOCOL INFORMATION

This is an open-label, single-sequence, one-way drug-drug interaction study to investigate the effect GSK3640254 has on the PK of a combination oral contraceptive containing EE and LNG. Effective contraception for women infected with human immunodeficiency virus (HIV) is important in the prevention of unplanned pregnancies.

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Pharmacokinetic concentration population will be used for concentration listing.	• Pharmacokinetic concentration population will be used for the PK concentration listings, summary tables, and plotting of concentration-time data.	• Align with reporting and analysis plan (RAP) 209712 and RAP 208134.
• Pharmacokinetic parameter population will be used for PK parameter listing, summary tables, and plotting of the concentration-time data and PK parameter summary	• Pharmacokinetic parameter population will be used for PK parameter listings, summary tables, and statistical analysis tables.	• Align with reporting and analysis plan (RAP) 209712 and RAP 208134.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To assess the effect of GSK3640254 on the steady state PK of EE and LNG under fed conditions in healthy female participants	• AUC(0-τ), Cmax, and Cτ for EE and LNG
Secondary Objectives	**Secondary Endpoints**
• To assess the effect of GSK3640254 on the PD of EE/LNG (suppression of ovulation as indicated by endogenous progesterone levels)	• Serum progesterone levels
• To assess the effect of GSK3640254 on LH and FSH	• Serum FSH and LH levels
• To characterize the steady state PK of GSK3640254 in the presence of EE/LNG	• AUC(0-τ), Cmax, Cτ, Tmax, and t1/2 for GSK3640254
• To Characterize the steady state PK of EE/LNG alone and in the presence of GSK3640254	• Tmax and t1/2 for EE and LNG
• To assess the safety and tolerability of GSK3640254 and EE/LNG when given in combination in healthy female participants	• Safety and tolerability parameters for AEs/SAEs, observed and change from baseline clinical laboratory assessments, ECGs, and vital sign measurements

AE = adverse event; AUC(0-τ) = area under the plasma concentration-time curve from time 0 to the end of the dosing interval at steady state; Cmax = maximum observed concentration; Cτ = Plasma concentration at the end of the dosing

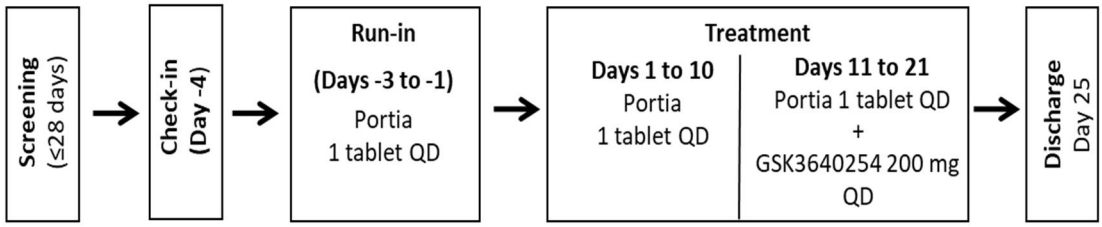
Objectives	Endpoints

interval; ECG = electrocardiogram; EE = ethinyl estradiol; FSH = follicle-stimulating hormone; LH = luteinizing hormone; LNG = levonorgestrel; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; t1/2 = apparent terminal phase half-life; Tmax = time of maximum observed concentration.

2.3. Study Design

Overview of Study Design and Key Features

Figure 1 Study Design Schematic



Design Features	• A phase 1, open-label, fixed-sequence, one-way drug-drug interaction study.
	• The study will consist of a screening period, check-in, a run-in period, a treatment period, and a follow-up period.
	  ○ Screening Period: up to 28 days before Day -4
	  ○ Check-in: Day -4
	  ○ Run-in Period: Portia (0.3 mg EE/0.15 mg LNG) once daily (QD) (Days -3 to -1)
	  ○ Treatment Period: Portia (0.03 mg EE/0.15 mg LNG) QD on Days 1 to 10 (Treatment A), followed by Portia (0.03 mg EE/0.15 mg LNG) QD coadministered with GSK3640254 200 mg on Days 11 to 21 (Treatment B)
	  ○ Follow-up Period[1]: 4 days
	• Approximately 25 participants will be treated to ensure that 20 evaluable participants complete the study.

Dosing	• Run-in Portia: Portia (0.03 mg EE/0.15 mg LNG) QD Days -3 to -1 • Treatment A: Portia (0.03 mg EE/0.15 mg LNG) QD on Days 1 to 10 • Treatment B: Portia (0.03 mg EE/0.15 mg LNG) QD coadministered with GSK3640254 200 mg on Days 11 to 21
Time & Events	• Refer to Appendix 1: Schedule of Activities
Treatment Assignment	• This is an open-label study. All eligible participants will receive the same treatment.
Interim Analysis	• No interim analysis is planned for this study

[1] The "Washout" period of this study should be called "Follow Up" as there is only one treatment period. See 208135 Protocol Clarification dated 10-June-2019

2.4. Statistical Hypotheses

The hypothesis tested by this study:

H_0: $\mu_{test}/\mu_{ref} < 0.8$ or $\mu_{test}/\mu_{ref} > 1.25$

H_a: $0.8 \leq \mu_{test}/\mu_{ref} \leq 1.25$

Where μ_{test} is the geometric least-squares mean for PK parameters of EE/LNG when coadministered with GSK3640254 and μ_{ref} is the geometric least-squares mean for PK parameters of EE/LNG when administered alone. If the null hypothesis is not rejected, then there is sufficient evidence to suggest an effect of GSK3640254 on the PK of EE/LNG; however, if the null hypothesis is rejected, then there is no evidence to suggest an effect of GSK3640254 on the PK of EE/LNG. The hypothesis test will be assessed using Schuirmann's 2 one-sided t-test procedure with α=0.05 for each test (Schuirmann, 1987). Each ratio will be compared to 0.8 and 1.25 as described above. Lack of effect is to be demonstrated if the 90% CIs for both LNG and EE lie within 0.8 and 1.25.

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 • This population will be used for screen failure listing and summary	• Study Population
Safety	• All participants who received at least 1 dose of study medication. • This population will be used for all demographic, disposition (exclude screen failure), and safety listings, summaries, and figure	• Study Population • Safety
Pharmacokinetic Concentration	• All participants who underwent plasma PK sampling and had evaluable PK assay results. • This population will be used for the PK concentration listings, summary tables, and plotting of concentration-time data.	• PK Concentration
Pharmacokinetic Parameter	• All participants who underwent plasma PK sampling and had evaluable PK parameters estimated. • This population will be used for PK parameter listings, summary tables, and statistical analysis tables.	• PK Parameter • PK statistical analysis
Pharmacodynamic Concentration	• All participants who underwent plasma PD sampling and had evaluable PD assay results. • This population will be used for the PD concentration listings, summary tables, and figures.	• PD Concentration

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 Protocol Deviation Management Plan. The “significant” protocol deviation in the Protocol Deviation Management Plan 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**
Portia (0.03 mg EE/0.15 mg LNG) QD on Days -3 to -1	Run-in Portia	1
Portia (0.03 mg EE/0.15 mg LNG) QD on Days 1 to 10	Treatment A	2
Portia (0.03 mg EE/0.15 mg LNG) QD coadministered with GSK3640254 200 mg on Days 11 to 21	Treatment B	3

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions), baseline for treatment A is defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits, before the dose of Portia on Day 1; baseline for treatment B is defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits, before the first dose on Day 11. If time is not collected, Day 1 or Day 11 assessments are assumed to be taken prior to the dose and used as baseline.

Parameter	Study Assessments Considered as Baseline					Baseline Used in Data Display	
	Screening	Day -4	Day 1 (Pre-Dose)	Day 10	Day 11 (Pre-Dose)	Treatment A	Treatment B
Safety							
Vital Sign	X	X	X	X	X	Day 1 (Pre-Dose)[1]	Day 11 (Pre-Dose)[1]
12-Lead ECG	X	X	X	X	X	Day 1 (Pre-Dose)	Day 11 (Pre-Dose)[1]
Hematology	X	X	X	X		Day 1 (Pre-Dose)	Day 10
Clinical Chemistry	X	X	X	X		Day 1 (Pre-Dose)	Day 10
Urinalysis	X	X	X	X		Day 1 (Pre-Dose)	Day 10

[1] The average (for quantitative assessments) or the worst case (for interpretation) of the predose 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 Phases and Treatment Emergent Adverse Events
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” 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). Plasma concentrations of EE, LNG, and GSK3640254 will be measured and reported.

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 WinNonlin (8.0 or higher). All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Cτ	Plasma concentration at the end of the dosing interval
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.

NOTES:

- Additional parameters may be included as required.

7.1.2. Summary Measure

AUC(0-τ), Cτ and Cmax at steady state following doses of 0.03 mg EE/0.15 mg LNG QD Days 1 through 10 in Treatment A and 0.03 mg EE/0.15 mg LNG QD coadministered with GSK3640254 200 mg QD on Days 11 through 21 in Treatment B in healthy female subjects.

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, graphically presented (where appropriate) and listed.

Primary plasma PK parameters (AUC(0-τ), Cτ, and Cmax) will be estimated for EE and LNG (Treatments A and B). Summary statistics (arithmetic mean, geometric mean, median, standard deviation (SD), minimum, maximum, and coefficient of variation) for plasma EE and LNG PK parameter values will be summarized by treatment.

Boxplots with overlaid individual values of primary plasma PK parameters for EE and LNG will be produced for subjects categorized by ALT (ALT level within normal range, ALT value is greater than upper limit of normal [ULN] but less than or equal to 3 times the ULN, and ALT level is greater than 3 times the ULN) and whether subjects met liver stopping criteria. Similarly, boxplots with overlaid individual values of primary plasma PK parameters will be produced by treatment with data presented according to subject's progesterone level (progesterone level is less than or equal to 6.36 nmol/L and progesterone level is greater than to 6.36 nmol/L) and whether subjects met liver stopping criteria.

7.1.4.1. Statistical Methodology Specification

The following PK statistical analyses will only be performed if sufficient data are available (i.e. if participants have well defined plasma profiles).

Endpoint / Variables
• Plasma primary PK endpoints include AUC(0-τ), Cτ, and Cmax for EE and LNG (Treatments A and B), as data permit
Model Specification
• Analyses will be performed on the natural logarithms of AUC(0-τ), Cτ and Cmax using linear mixed-effect models with treatment as a fixed effect, participants as random effect, and measurements within participant as repeated measures. • Effects will be estimated, and confidence intervals (CIs) will be constructed for the following treatment comparisons: Treatment B versus Treatment A • Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale.
Model Checking & Diagnostics
• Model assumptions will be applied, but appropriate adjustments may be made based on the data.
Model Results Presentation
• Statistical analysis by analysis of variance (ANOVA) will be presented in tabular format with geometric mean ratios for: Treatment B versus Treatment A

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 Pharmacokinetic).

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 WinNonlin (8.0 or higher). All calculations of non-compartmental parameters will be based on actual sampling times.

Plasma pharmacokinetic parameters listed below will be determined from the total plasma concentration-time data, as data permits.

Parameter	Parameter Description
Cmax	Maximum observed concentration, determined directly from the concentration-time data. (GSK3640254 only)
C_τ	Plasma concentration at the end of the dosing interval (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)
Tmax	Time of maximum observed concentration
t1/2	Apparent terminal phase half-life

NOTES:

- Additional parameters may be included as required.

7.2.2. Summary Measure

Ethinyl estradiol and LNG Tmax, and t1/2 at steady state following doses of 0.03 mg EE/0.15 mg LNG QD Days 1 through 10 in Treatment A and 0.03 mg EE/0.15 mg LNG QD coadministered with GSK3640254 200 mg QD on Days 11 through 21 in Treatment B in healthy female subjects.

GSK3640254 AUC(0-τ), Cτ, Cmax, Tmax, and t1/2 at steady state following doses of 0.03 mg EE/0.15 mg LNG QD coadministered with GSK3640254 200 mg QD on Days 11 through 21 in Treatment B in healthy female subjects.

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 and statistical analysis, 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 will be summarized using descriptive statistics, graphically presented (where appropriate), and listed.

Secondary plasma PK parameters (Tmax and t1/2) will be estimated for EE and LNG (Treatments A and B) and secondary plasma PK parameters AUC(0- τ), Cτ, Cmax, Tmax, and t1/2 will be estimated for GSK3640254 (Treatment B). Summary statistics (arithmetic mean, geometric mean, median, SD, minimum, maximum, and coefficient of variation) for secondary plasma PK parameters of GSK3640254 and EE and LNG will be summarized by treatment.

Predose (trough) PK plasma concentrations (EE and LNG: Days 9, 10, 11 [Treatment A], 19 through 21 and the 24-hour post-Day 21 dose [Treatment B]; GSK3640254: Days 19 through 21 and the 24-hour post-Day 21 dose [Treatment B]) will be summarized using the PK Concentration Population and used to assess achievement of steady state.

Boxplots with overlaid individual values of primary plasma PK parameters for GSK3640254 will be produced for subjects categorized by ALT (ALT level within normal range, ALT value is greater than upper limit of normal [ULN] but less than or equal to 3 times the ULN, and ALT level is greater than 3 times the ULN) and whether subjects met liver stopping criteria. Similarly, boxplots with overlaid individual values of primary plasma PK parameters will be produced by treatment with data presented according to subject's progesterone level (progesterone level is less than or equal to 6.36 nmol/L and progesterone level is greater than to 6.36 nmol/L) and whether subjects met liver stopping criteria.

8. PHARMACODYNAMIC ANALYSES

8.1. Endpoint / Variables

Serum LH, FSH, and progesterone levels when EE/LNG is administered alone and in combination with GSK3640254.

8.2. Summary Measures

Serum LH, FSH, and progesterone levels.

8.3. Population of Interest

The PD analyses will be based on the "Pharmacodynamic Concentration" population, unless otherwise specified.

8.4. Statistical Analysis / 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.

Individual concentration-time profiles will be created for LH, FSH and progesterone. For each parameter, the profiles for both treatments will be overlaid on the same plot.

Actual values for serum LH, FSH, and progesterone levels will be listed and summarized by treatment using descriptive statistics; in addition, the mean value with the SD will be presented in a figure. The maximum LH and FSH concentration of each treatment period will be identified for each subject and listed with treatment and day and summarized by treatment.

For each parameter (LH, FSH, and progesterone), the concentrations will be plotted by treatment and timepoint using box-plots displaying the median, range, 25^{th} and 75^{th} percentiles. Maximum LH and FSH will be plotted within the same figure.

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.

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 plotted versus time. The details of the planned displays are in Appendix 9: List of Data Displays.

9.3. 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. A figure of mean change from baseline in QTcF interval along with the 2-sided 95% CI using Student's t distribution will be presented by treatment and visit. The details of the planned displays are presented in Appendix 9: List of Data Displays.

10. REFERENCES

Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinetics Biopharm. 1987; 15(6): 657-80.

ViiV Healthcare group of companies Document Number 2018N383291_00 (10-MAY-2019): The Effect of Coadministration of GSK3640254 on the Pharmacokinetics of a Combined Oral Contraceptive Containing Ethiny Estradiol and Levonorgestrel in Healthy Female Subjects.208135 Protocol Clarification (10-JUN-2019).

11. APPENDICES

11.1. Appendix 1: Schedule of Activities

11.1.1. Protocol Defined Schedule of Events

Screening Visit

Procedure	Screening (up to 28 days before Day -4)
Outpatient visit	X
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 (ECG)	X
Vital sign measurements	X
Medication/drug/alcohol history	X
Past and current medical conditions	X
Columbia Suicide Severity Rating Scale (C-SSRS)	X
Serum pregnancy test	X
Drug, alcohol, and cotinine screen	X
Human immunodeficiency virus (HIV), Hepatitis B and C screening	X

[1.] A full physical examination will include at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal (GI), and neurological systems.

Table 2 Time and Events Table

Procedure	Check-in	Run-in			Treatment										Washout [1]				Notes
	D -4	D -3	D -2	D -1	D 1	D 2-9	D 10 [2]	D 11	D 12	D 13	D 14-18	D 19	D 20	D 21	D 22	D 23	D 24 [3]	D 25	
Admit to clinic	X																		
Discharge from clinic																		X	
Brief physical examination	X						X										X		A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen.
Vital signs	X				X		X	X			D15			X			X		Obtained before dosing, where applicable. Blood pressure and pulse will be measured in triplicate when they occur at the same time point as clinical laboratory assessments.
12-lead ECG	X				X		X	X			D15			X			X		On Day 11, triplicate ECGs will be taken before dosing. On Day 11, single ECGs will be taken at 2, 4, and 6 hours after dosing. On Day 15, single ECGs will be taken at 2, 4, and 6 hours after dosing. Single ECGs will be taken on other scheduled days.

Procedure	Check-in	Run-in			Treatment										Washout [1]				Notes
	D -4	D -3	D -2	D -1	D 1	D 2-9	D 10 [2]	D 11	D 12	D 13	D 14-18	D 19	D 20	D 21	D 22	D 23	D 24 [3]	D 25	
Drug, alcohol, and cotinine screen	X																		See Protocol Appendix 2 for specific tests to be performed.
Laboratory assessments (hematology, chemistry, urinalysis tests)	X				X		X							X			X		See Protocol Appendix 2 for specific tests to be performed. Taken before dosing, where applicable.
Pregnancy test	X			X			X										X		
Genetic sample (optional)	X																		
C-SSRS								X						X					
Study intervention: Portia (0.03 mg EE/ 0.15 mg LNG)		X	X	X	X	X	X	X	X	X	X	X	X	X					
Study intervention: GSK3640254 200 mg								X	X	X	X	X	X	X					
Trough PK sampling: EE and LNG						D9						X	X						PK sample collected before dosing.

Procedure	Check-in	Run-in			Treatment										Washout [1]				Notes
	D -4	D -3	D -2	D -1	D 1	D 2-9	D 10 [2]	D 11	D 12	D 13	D 14-18	D 19	D 20	D 21	D 22	D 23	D 24 [3]	D 25	
Serial PK sampling: EE and LNG							X	X						X	X	X	X		PK samples will be collected predose and after dosing at 15 and 30 minutes and 1, 1.5, 2, 3, 4, 7, 12, and 24 hours relative to Day 10 dosing. The 24-hour post-dose sample should be taken prior to dosing on Day 11. PK samples will be collected predose and after dosing at 15 and 30 minutes and 1, 1.5, 2, 3, 4, 7, 12, 24, 48, and 72 hours relative to Day 21 dosing.
Trough PK sampling: GSK3640254												X	X						PK sample collected before dosing.
Serial PK sampling: GSK3640254														X	X	X	X	X	PK samples will be collected predose and after dosing at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 72, and 96 hours relative to Day 21 dosing.
PD sampling: LH, FSH, progesterone					X		X	X						X	X				Samples collected before dosing.
AE review		←==========→																	
SAE review	←==========→																		

Procedure	Check-in	Run-in			Treatment										Washout [1]				Notes
	D -4	D -3	D -2	D -1	D 1	D 2-9	D 10 [2]	D 11	D 12	D 13	D 14-18	D 19	D 20	D 21	D 22	D 23	D 24 [3]	D 25	
Concomitant medication review	←==========→																		

AE = adverse event; D = Day; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EE = ethinyl estradiol; FSH = follicle-stimulating hormone; LH = luteinizing hormone; LNG = levonorgestrel; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event.

1 Washout period refers to follow-up period. See 208135 Protocol Clarification dated 10-Jun-2019.

2 Assessments performed on Day 10 will be considered Baseline for GSK3640254 dosing.

3 Evaluations scheduled for Day 24 will also be performed for participants who discontinue early.

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).

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

11.2.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before Day -4
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 adverse events. 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\mid208135\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 adopted for reporting of data based on the raw data collected, unless otherwise stated. • 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 pharmacokinetic 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, 90% CI of arithmetic mean, geometric mean, 95% CI of geometric mean, SD, SD of logged data CV (%), and between-subject geometric coefficient of variation (CVb (%)) will be reported. CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = 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 -3
  → Period Day = Assessment Date – Dose Date on Day -3
  • Dose Day on Day -3 <= Assessment Date < Dose Date on Day 1
  → Period Day = Assessment Date – Dose Date on Day -3 + 1
  • Dose Date on Day 1 <= Assessment Date < First Dose Date on Day 11
  → Period Day = Assessment Date – Dose Date on Day 1 + 1
  • Assessment Date >= First Dose Date on Day 11
  → Period Day = Assessment Date – First Dose Date on Day 11 + 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:
  ○ Any participant with a missing day will have this imputed as day '15'.
  ○ 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
• Adverse events of special interest include all AEs classified in the cardiovascular (per MedDRA) system organ class, seizure, and syncope.

12-Lead Electrocardiograms
QTcF Interval
• QTcF interval will be collected on the eCRF. If QTcF interval is missing on the eCRF, the value in msec will be calculated using QT interval (msec) and heart rate (bpm as $\mathrm{QTCF} = \frac{QT}{\sqrt[3]{60/Heart\ \ Rate}}$
QTcB Interval
• QTcB interval in msec will be calculated using QT interval (msec) and heart rate (bpm) as $QTCB = \frac{QT}{\sqrt{60/Heart\ \ Rate}}$

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 were not 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: ○ 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. ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be 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.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Lymphocyte Count, Low (cell/mm^3; cells/L) > 5 years of age (not HIV infected)	600 to < 650 0.600 × 10^9 to < 0.650 × 10^9	500 to < 600 0.500 × 10^9 to < 0.600 × 10^9	350 to < 500 0.350 × 10^9 to < 0.500 × 10^9	< 350 < 0.350 × 10^9
Absolute Neutrophil Count, Low (cells/mm^3; cells/L) > 7 days of age	800 to 1,000 0.800 × 10^9 to 1.000 × 10^9	600 to 799 0.600 × 10^9 to 0.799 × 10^9	400 to 599 0.400 × 10^9 to 0.599 × 10^9	< 400 < 0.400 × 10^9
Hemoglobin, Low (g/dL; mmol/L) ≥ 13 years of age (male only)	10.0 to 10.9 6.19 to 6.76	9.0 to < 10.0 5.57 to < 6.19	7.0 to < 9.0 4.34 to < 5.57	< 7.0 <4.34
Hemoglobin, Low (g/dL; mmol/L) ≥ 13 years of age (female only)	9.5 to 10.4 5.88 to 6.48	8.5 to < 9.5 5.25 to < 5.88	6.5 to < 8.5 4.03 to < 5.25	< 6.5 < 4.03
Platelets, Decreased (cells/mm^3; cells/L)	100,000 to < 125,000 100.000 × 10^9 to < 125.000 × 10^9	50,000 to < 100,000 50.000 × 10^9 to < 100.000 × 10^9	25,000 to < 50,000 25.000 × 10^9 to < 50.000 × 10^9	< 25,000 < 25.000 × 10^9
White Blood Cell, Decreased (cells/mm^3; cells/L) > 7 days of age	2,000 to 2,499 2.000 × 10^9 to 2.499 × 10^9	1,500 to 1,999 1.500 × 10^9 to 1.999 × 10^9	1,000 to 1,499 1.000 × 10^9 to 1.499 × 10^9	< 1,000 < 1.000 × 10^9

Clinical Chemistry				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Albumin, Low (g/dL; g/L)	3.0 to < LLN 30 to < LLN	≥ 2.0 to < 3.0 ≥ 20 to < 30	< 2.0 < 20	NA
Alkaline Phosphatase, High	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Alanine Aminotransferase, High	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 ULN
Amylase (Total), High	1.1 to < 1.5 × ULN	1.5 to < 3.0 × ULN	3.0 to < 5.0 × ULN	≥ 5.0 × ULN
Aspartate Aminotransferase, High	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Bicarbonate, Low (mEq/L; mmol/L)	16.0 to < LLN 16.0 to < LLN	11.0 to < 16.0 11.0 to < 16.0	8.0 to < 11.0 8.0 to < 110.	< 8.0 < 8.0
Direct Bilirubin, High > 28 days of age	NA	NA	> ULN with other signs and symptoms of hepatotoxicity	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
Total Bilirubin, High > 28 days of age	1.1 to < 1.6 × ULN	1.6 to < 2.6 × ULN	2.6 to < 5.0 × ULN	≥ 5.0 × ULN
Calcium, High (mg/dL; mmol/L) ≥ 7 days of age	10.6 to < 11.5 2.65 to < 2.88	11.5 to < 12.5 2.88 to < 3.13	12.5 to < 13.5 3.13 to < 3.38	≥ 13.5 ≥ 3.38
Calcium, Low (mg/dL; mmol/L) ≥ 7 days of age	7.8 to < 8.4 1.95 to < 2.10	7.0 to < 7.8 1.75 to < 1.95	6.1 to < 7.0 1.53 to < 1.75	< 6.1 < 1.53
Creatine Kinase, High	3 to < 6 × ULN	6 to < 10 × ULN	10 to < 20 × ULN	≥ 20 × ULN
Creatinine, High *Choose the method that selects for the higher grade*	1.1 to 1.3 × ULN	> 1.3 to 1.8 × ULN OR Increase to 1.3 to < 1.5 × participant's baseline	> 1.8 to < 3.5 ULN OR Increase to 1.5 to < 2.0 × participant's baseline	≥ 3.5 × ULN OR Increase of ≥ 2.0 × participant's baseline
Glucose Fasting, High (mg/dL; mmol/L)	110 to 125 6.11 to < 6.95	> 125 to 250 6.95 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75
Glucose, Low (mg/dL; mmol/L) ≥ 1 month of age	55 to 64 3.05 to < 3.55	40 to < 55 2.22 to < 3.05	30 to < 40 1.67 to < 2.22	< 30 < 1.67
Lipase, High	1.1 to < 1.5 × ULN	1.5 to < 3.0 × ULN	3.0 to < 5.0 × ULN	≥ 5.0 × ULN
Cholesterol, Fasting, High (mg/dL; mmol/L) ≥ 18 years of age	200 to < 240 5.18 to < 6.19	240 to < 300 6.19 to < 7.77	≥ 300 ≥ 7.77	NA
Triglycerides, Fasting, High (mg/dL; mmol/L)	150 to 300 1.71 to 3.42	> 300 to 500 > 3.42 to 5.7	> 500 to < 1.000 > 5.7 to 11.4	> 1,000 > 11.4
Phosphate, Low (mg/dL; mmol/L) > 14 years of age	2.0 to < LLN 0.65 to < LLN	1.4 to < 2.0 0.45 to < 0.65	1.0 to < 1.4 0.32 to < 0.45	< 1.0 < 0.32

Clinical Chemistry				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Potassium, High (mEq/L; mmol/L)	5.6 to < 6.0 5.6 to < 6.0	6.0 to < 6.5 6.0 to < 6.5	6.5 to < 7.0 6.5 to < 7.0	≥ 7.0 ≥ 7.0
Potassium, Low (mEq/L; mmol/L)	3.0 to < 3.4 3.0 to < 3.4	2.5 to < 3.0 2.5 to < 3.0	2.0 to < 2.5 2.0 to < 2.5	< 2.0 < 2.0
Sodium, High (mEq/L; mmol/L)	146 to < 150 146 to < 150	150 to < 154 150 to < 154	154 to < 160 154 to < 160	≥ 160 ≥ 160
Sodium, Low (mEq/L; mmol/L)	130 to < 135 130 to < 135	125 to < 130 125 to < 130	121 to < 125 121 to < 125	≤ 120 ≤ 120
Uric Acid, High (mEq/L; mmol/L)	7.5 to < 10.0 0.45 to < 0.59	10.0 to < 12.0 0.59 to < 0.71	12.0 to < 15.0 0.71 to < 0.89	≥ 15.0 ≥ 0.89

NA=not applicable; LLN = lower limit of normal; ULN=upper limit of normal.

Urinalysis				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Glucose/Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Protein/Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA
Red Blood Cells (RBCs)/Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR with RBC casts OR intervention indicated	Life-threatening consequences

NA=not applicable

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	<320	>450
Absolute PR Interval	msec	< 120	> 200
Absolute QRS Interval	msec	< 60	> 120
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
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
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
Cmax	Maximum Observed Concentration
C-SSRS	Columbia Suicide Severity Rating Scale
Cτ	Plasma Concentration at the End of the Dosing Interval
CV_b	Coefficient of Variation (Between)
DBF	Database Freeze
DBR	Database Release
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EE	Ethinyl Estradiol
FSH	Follicle-Stimulating Hormone
GSK	GlaxoSmithKline
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
LH	Luteinizing Hormone
LLN	Lower Limit of Normal
LNG	Levonorgestrel
PD	Pharmacodynamic
PK	Pharmacokinetic
QD	Once Daily
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
Tmax	Time of Maximum Observed Concentration
ULN	Upper Limit of Normal

11.8.2. Trademarks

Trademarks of the ViiV Group of Companies
NONE

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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 1.9	
Safety	2.1 to 2.27	2.1 to 2.6
Pharmacokinetic	3.1 to 3.14	3.1 to 3.21
Pharmacodynamic	4.1 to 4.2	4.1 to 4.3
Section	**Listings**	
ICH Listings	1 to 32	
Other Listings	33 to 40	

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
Pharmacodynamic	PD_Fn	PD_Tn	PD_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.	Safety	NS1	Summary of Number of Subjects Enrolled by Country and Site ID		SAC
1.2.	Safety	ES1	Summary of Subject Disposition for the Subject Conclusion Record		SAC
1.3.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC
1.4.	Screened	SD1	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
Exposure					
1.9.	Safety	EX1	Summary of Exposure to Study Treatment		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
2.20.	Safety	AE1CP	Summary of Adverse Events of Special Interest		SAC
Laboratory: Chemistry					
2.7.	Safety	LB1	Summary of Clinical Chemistry Changes from Baseline		SAC
2.21.	Safety	LB1	Summary of Clinical Chemistry Values		SAC
2.8.	Safety	LB16	Summary of Clinical Chemistry Results by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC
Laboratory: Hematology					
2.9.	Safety	LB1	Summary of Hematology Changes from Baseline		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.22.	Safety	LB1	Summary of Hematology Values		SAC
2.10.	Safety	LB16	Summary of Hematology Results by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC
Laboratory: Urinalysis					
2.11.	Safety	UR3	Summary of Urinalysis Dipstick Results		SAC
2.12.	Safety	LB1	Summary of Urine Concentration Changes from Baseline		SAC
2.23.	Safety	LB1	Summary of Urine Concentration Values		SAC
2.13.	Safety	LB16	Summary of Urinalysis by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC
ECG					
2.14.	Safety	SAFE_T1	Summary of ECG Findings		SAC
2.15.	Safety	EG2	Summary of ECG Changes from Baseline		SAC
2.24	Safety	EG2	Summary of ECG Values		SAC
2.16.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		SAC
2.17.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		SAC
Vital Signs					
2.18.	Safety	VS1	Summary of Vital Sign Changes from Baseline		SAC
2.25.	Safety	VS1	Summary of Vital Sign Values		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
C-SSRS					
2.19.	Safety	CSSRS4	Listing of C-SSRS Suicidal Ideation and Behavior Data	Only include participants who have suicidal ideation or behavior	SAC
Liver Event					
2.26.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC
2.27.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		SAC

11.9.6. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
2.1.	Safety	EG9	Mean (95% CI) Change from Baseline in QTcF Interval by Timepoint and Treatment		SAC
Laboratory					
2.2.	Safety	LB11	Alanine Aminotransferase by Time		SAC
2.3.	Safety	LB11	Aspartate Aminotransferase by Time		SAC
2.4.	Safety	LB11	Alkaline Phosphatase by Time		SAC
2.5.	Safety	LB11	Total Bilirubin by Time		SAC
2.6.	Safety	LB11	Gamma-Glutamyl Transferase by Time		SAC

11.9.7. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
3.1.	PK Concentration	PKCT1	Summary of Ethinyl Estradiol (EE) Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment		SAC
3.2.	PK Concentration	PKCT1	Summary of Levonorgestrel (LNG) Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment		SAC
3.3.	PK Concentration	PKCT1	Summary of GSK3640254 Plasma Pharmacokinetic Concentration-Time Data (units) by Treatment		SAC
3.4.	PK Concentration	PKCT1	Summary of Predose (trough) Ethinyl Estradiol (EE) Plasma Concentration Data (units) by Treatment		SAC
3.5.	PK Concentration	PKCT1	Summary of Predose (trough) Levonorgestrel (LNG) Plasma Concentration Data (units) by Treatment		SAC
3.6.	PK Concentration	PKCT1	Summary of Predose (trough) GSK3640254 Plasma Concentration Data (units) by Treatment		SAC
PK Derived Parameters					
3.7.	PK Parameter	PKPT4	Summary Statistics of Derived Ethinyl Estradiol (EE) Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.8.	PK Parameter	PKPT4	Summary Statistics of Derived Ethinyl Estradiol (EE) Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.9.	PK Parameter	PKPT4	Summary Statistics of Derived Levonorgestrel (LNG) Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.10.	PK Parameter	PKPT4	Summary Statistics of Derived Levonorgestrel (LNG) Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.11.	PK Parameter	PKPT4	Summary Statistics of Derived GSK3640254 Plasma Pharmacokinetic Parameters (Non-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
3.12.	PK Parameter	PKPT4	Summary Statistics of Derived GSK3640254 Plasma Pharmacokinetic Parameters (Ln-Transformed) Based on Actual Time by Treatment	Parameters with units	SAC
PK Analysis Tables					
3.13.	PK Parameter	PKPT3	Statistical Analysis of Ethinyl Estradiol (EE) Plasma Pharmacokinetic Parameters: Analysis of Variance (ANOVA)	AUC(0-τ), Cτ, and Cmax	SAC
3.14.	PK Parameter	PKPT3	Statistical Analysis of Levonorgestrel (LNG) Plasma Pharmacokinetic Parameters: Analysis of Variance (ANOVA)	AUC(0-τ), Cτ, and Cmax	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 Ethinyl Estradiol (EE) Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ Treatments Overlaid	SAC
3.2.	PK Concentration	PKCF1P	Individual Levonorgestrel (LNG) Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ Treatments Overlaid	SAC
3.3.	PK Concentration	PKCF1P	Individual GSK3640254 Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant Dashed line represents the LLQ	SAC
3.4.	PK Concentration	PKCF1P	Individual Ethinyl Estradiol (EE) Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ Individual Overlaid	SAC
3.5.	PK Concentration	PKCF1P	Individual Levonorgestrel (LNG) Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment Dashed line represents the LLQ Individual Overlaid	SAC
3.6.	PK Concentration	PKCF1P	Individual GSK3640254 Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Dashed line represents the LLQ Individual Overlaid	SAC
Mean / Median Concentration Plots					
3.7.	PK Concentration	PKCF2	Mean (± Standard Deviation) Ethinyl Estradiol (EE) Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.8.	PK Concentration	PKCF2	Mean (± Standard Deviation) Levonorgestrel (LNG) Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.9.	PK Concentration	PKCF2	Mean (± Standard Deviation) GSK3640254 Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)		SAC
3.10.	PK Concentration	PKCF3	Median (Range) Ethinyl Estradiol (EE) Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.11.	PK Concentration	PKCF3	Median (Range) Levonorgestrel (LNG) Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	Treatments Overlaid	SAC
3.12.	PK Concentration	PKCF3	Median (Range) GSK3640254 Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)		SAC
3.13.	PK Concentration	PKCF2	Mean (± Standard Deviation) Predose (Trough) Ethinyl Estradiol (EE) Plasma Concentration Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment	SAC
3.14.	PK Concentration	PKCF2	Mean (± Standard Deviation) Predose (Trough) Levonorgestrel (LNG) Plasma Concentration Plots by Treatment (Linear and Semi-Logarithmic)	Paginate by Treatment	SAC
3.15.	PK Concentration	PKCF2	Mean (± Standard Deviation) Predose (Trough) GSK3640254 Plasma Concentration Plots by Treatment (Linear and Semi-Logarithmic)		SAC
3.16.	PK Parameter	PK_F1	Boxplot of Ethinyl Estradiol (EE) Pharmacokinetic Parameters Categorized by Alanine Aminotransferase		SAC
3.17.	PK Parameter	PK_F1	Boxplot of Levonogrestrel (LNG) Pharmacokinetic Parameters Categorized by Alanine Aminotransferase		SAC
3.18.	PK Parameter	PK_F1	Boxplot of GSK3640254 Pharmacokinetic Parameters Categorized by Alanine Aminotransferase		SAC
3.19.	PK Parameter	PK_F2	Boxplot of Ethinyl Estradiol (EE) Pharmacokinetic Parameters Categorized by Progesterone		SAC
3.20.	PK Parameter	PK_F2	Boxplot of Levonogrestrel (LNG) Pharmacokinetic Parameters Categorized by Progesterone		SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.21.	PK Parameter	PK_F3	Boxplot of GSK3640254 Pharmacokinetic Parameters Categorized by Progesterone		SAC

11.9.9. Pharmacodynamic Table

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1	PD Concentration	PD_T1	Summary of Serum Luteinizing Hormone, Follicle-Stimulating Hormone, and Progesterone Concentration		SAC
4.2	PD Concentration	PD_T1	Summary of Maximum Serum Luteinizing Hormone and Follicle-Stimulating Hormone Concentration		SAC

11.9.10. Pharmacodynamic Figure

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1	PD Concentration	PD_F1	Individual Serum Luteinizing Hormone, Follicle-Stimulating Hormone, and Progesterone Concentration by Participant		SAC
4.2	PD Concentration	PD_F2	Mean (± Standard Deviation) Serum Luteinizing Hormone, Follicle-Stimulating Hormone, and Progesterone Concentration by Visit and Treatment		SAC
4.3	PD Concentration	PD_F3	Boxplot of Serum Luteinizing Hormone, Follicle-Stimulating Hormone, and Progesterone Concentration		SAC

11.9.11. 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					
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

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
14.	Safety	AE9CP	Listing of All Adverse Events		SAC
42.	Safety	AE9CP	Listing of Adverse Events of Special Interest		SAC
Serious and Other Significant Adverse Events					
15.	Safety	AE9CP	Listing of Study Drug Related Adverse Events		SAC
16.	Safety	AE9CP	Listing of Serious Adverse Events (Fatal & Non-Fatal)		SAC
17.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
18.	Safety	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study		SAC
19.	Safety	PREG1b	Listing of Subjects Who Became Pregnant During the Study		SAC
Hepatobiliary (Liver)					
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
43	Safety	VS5	Listing of Vital Results for Subjects with Liver Stopping Events		SAC
44	Safety	LIVER5	Listing of Subjects with Liver Monitoring/Stopping Event Reporting		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

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
27.	Safety	LB5A	Listing of All Urinalysis Data for Subjects with any Toxicities		SAC
28.	Safety	LB5A	Listing of Pregnancy Test Results		SAC
ECG					
29.	Safety	EG6	Listing of All ECG Findings		SAC
30.	Safety	EG6	Listing of All Abnormal ECG Findings		SAC
31.	Safety	EG4	Listing of All ECG Values		SAC
Vital Signs					
32.	Safety	VS5	Listing of All Vital Signs of Potential Clinical Importance		SAC
33.	Safety	VS5	Listing of All Vital Signs for Subjects with any Value of Potential Clinical Importance		SAC

11.9.12. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetics					
34.	PK Concentration	PKCL1P	Listing of Ethinyl Estradiol (EE) Plasma Concentration-Time Data by Treatment		SAC
35.	PK Concentration	PKCL1P	Listing of Levonorgestrel (LNG) Plasma Concentration-Time Data by Treatment		SAC
36.	PK Concentration	PKCL1P	Listing of GSK3640254 Plasma Concentration-Time Data by Treatment		SAC
37.	PK Parameter	PKPL1P	Listing of Ethinyl Estradiol (EE) Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment		SAC
38.	PK Parameter	PKPL1P	Listing of Levonorgestrel (LNG) Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment		SAC
39.	PK Parameter	PKPL1P	Listing of GSK3640254 Plasma Pharmacokinetic Parameters Based on Actual Time by Treatment		SAC
Pharmacodynamics					
40.	PD Concentration	PD_L1	Listing of Serum Luteinizing Hormone, Follicle-Stimulating Hormone, and Progesterone Concentration		SAC
41.	PD Concentration	PD_L1	Listing of Maximum Serum Luteinizing Hormone and Follicle-Stimulating Hormone Concentration by Treatment		SAC