TITLE PAGE

Protocol Title: The Effect of Coadministration of GSK3640254 on the Pharmacokinetics of a Combined Oral Contraceptive Containing Ethinyl Estradiol and Levonorgestrel in Healthy Female Subjects

Protocol Number: 208135

Compound Number: GSK3640254

Study Phase: Phase I

Short Title: Effect of GSK3640254 on the Pharmacokinetics of a Combination Oral Contraceptive

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In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Vice President, Global Research and Medical Strategy

This study is sponsored by ViiV Healthcare. PPD with GlaxoSmithKline are supporting ViiV Healthcare in the conduct of this study.

Medical Monitor Name and Contact Information: Can be found in the Study Reference Manual

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SPONSOR SIGNATORY:

PPD

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: The Effect of Coadministration of GSK3640254 on the Pharmacokinetics of a Combined Oral Contraceptive Containing Ethinyl Estradiol and Levonorgestrel in Healthy Female Subjects

Short Title: Effect of GSK3640254 on the Pharmacokinetics of a Combination Oral Contraceptive

Rationale: This is an open-label, single-sequence, 1-way drug-drug interaction (DDI) study to investigate the effect GSK3640254 has on the pharmacokinetics (PK) of a combination oral contraceptive containing ethinyl estradiol (EE) and levonorgestrel (LNG). Effective contraception for women infected with human immunodeficiency virus (HIV) is important in the prevention of unplanned pregnancies.

Objectives and Endpoints:

Objectives	Endpoints
Primary • To assess the effect of GSK3640254 on the steady state PK of EE and LNG under fed conditions in healthy female participants	The primary PK endpoints are: • AUC(0-τ), Cmax, and Cτ for EE and LNG
Secondary • To assess the effect of GSK3640254 on the PD of EE/LNG (suppression of ovulation as indicated by endogenous progesterone levels) • To assess the effect of GSK3640254 on LH and FSH • To characterize the steady state PK of GSK3640254 in the presence of EE/LNG • To characterize the steady state PK of EE/LNG alone and in the presence of GSK3640254 • To assess the safety and tolerability of GSK3640254 and EE/LNG when given in combination in healthy female participants	The secondary endpoints are: • Serum progesterone levels • Serum FSH and LH levels • AUC(0-τ), Cmax, Cτ, Tmax, and t1/2 for GSK3640254 • Tmax and t1/2 for EE and LNG • 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 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.

Overall Design: This is a Phase 1, open-label, fixed-sequence, 1-way DDI study designed to assess the PK, pharmacodynamics (PD), safety, and tolerability of GSK3640254 and an oral contraceptive containing EE/LNG (Portia) when administered alone and in combination in healthy female participants.

The study will consist of a screening period, check-in, a run-in period, and a treatment period with Portia given alone and in combination with GSK3640254. Participants will be screened within 28 days before check-in (Day -4).

Participants should take Portia in the morning at approximately the same time throughout study participation. During the treatment period, the participants will fast overnight for at least 8 hours prior to GSK3640254 dosing and will receive a moderate fat meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption.

Blood samples for the analysis of EE and LNG will be collected before dosing on Days 9 to 10 and 19 to 21, and up to 24 and 72 hours after dosing on Days 10 and 21 of the treatment period, respectively. Blood samples for the analysis of GSK3640254 will be collected before dosing on Days 19 to 21, and up to 96 hours after dosing on Day 21 of the treatment period.

Blood samples for the analysis of progesterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) will be collected on Days 1, 10, 11, 21, and 22 of the treatment period.

Safety and tolerability will be assessed by monitoring and recording of adverse events, clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

Study assessments will be performed as indicated in the Schedule of Activities (SoA). Participants will check into the clinic on Day -4 and will remain confined until discharge on Day 25.

Disclosure Statement: This is a single group, single arm study that has no masking.

Number of Participants: Approximately 25 participants will be treated to ensure that 20 evaluable participants complete the study.

Intervention Groups and Duration: The treatments will be as follows:

- Run-in Period: Portia (0.03 mg EE/0.15 mg LNG) once daily (QD) Days -3 to -1
- Treatment A: Portia (0.03 mg EE/0.15 mg LNG) QD on Days 1 to 10 of the treatment period
- Treatment B: Portia (0.03 mg EE/0.15 mg LNG) QD coadministered with GSK3640254 200 mg on Days 11 to 21 of the treatment period

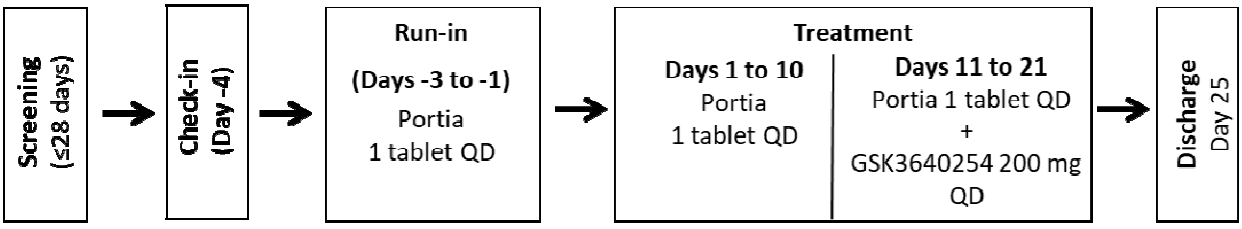
The duration of the study, including Screening and Run-in, is approximately 8 weeks.

Data Monitoring Committee: No

1.2. Schema

A summary of the overall study design is presented in Figure 1.

Figure 1 Study Design Schematic



1.3. Schedule of Activities (SoA)

- Screening procedures may be done over more than one visit, but must all be completed within 28 days prior to check-in.
- The following demographic parameters will be captured: year of birth, sex, race and ethnicity.
- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria.

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.

Time and Events Table

Procedure	Check-in	Run-in			Treatment										Washout				Notes
	D -4	D -3	D -2	D -1	D 1	D 2-9	D 10 [1]	D 11	D 12	D 13	D 14-18	D 19	D 20	D 21	D 22	D 23	D 24 [2]	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				Notes
	D -4	D -3	D -2	D -1	D 1	D 2-9	D 10 [1]	D 11	D 12	D 13	D 14-18	D 19	D 20	D 21	D 22	D 23	D 24 [2]	D 25	
Drug, alcohol, and cotinine screen	X																		See Appendix 2 for specific tests to be performed.
Laboratory assessments (hematology, chemistry, urinalysis tests)	X				X		X							X			X		See 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				Notes
	D -4	D -3	D -2	D -1	D 1	D 2-9	D 10 [1]	D 11	D 12	D 13	D 14-18	D 19	D 20	D 21	D 22	D 23	D 24 [2]	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				Notes
	D -4	D -3	D -2	D -1	D 1	D 2-9	D 10 [1]	D 11	D 12	D 13	D 14-18	D 19	D 20	D 21	D 22	D 23	D 24 [2]	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 Assessments performed on Day 10 will be considered Baseline for GSK3640254 dosing.

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

- The timing and number of planned study assessments, including safety, pharmacokinetic (PK), pharmacodynamic (PD), 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/PD 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).

2. INTRODUCTION

2.1. Study Rationale

This is an open-label, single-sequence, 1-way drug-drug interaction (DDI) study to investigate the effect GSK3640254 has on the PK of a combination oral contraceptive containing ethinyl estradiol (EE) and levonorgestrel (LNG). Effective contraception for women infected with human immunodeficiency virus (HIV) is important in the prevention of unplanned pregnancies.

2.2. Background

GSK3640254 is an HIV maturation inhibitor (MI) which is improved over prior developmental MIs in the following ways: (1) it exhibits significantly improved pan-genotypic coverage and potency against polymorphic variants; (2) *in vitro* data suggest that GSK3640254 exhibits a higher barrier to emergence of resistant viruses (except for A364V); (3) GSK3640254 has improved potency *in vitro* toward all HIV-1 subtypes; (4) it has potential for improved gastrointestinal (GI) tolerability; and (5) it has a projected lower once-daily human dose. Summaries of the pre-clinical and clinical studies are included in the Clinical Investigator's Brochure (CIB) [GSK Document Number 2018N379610_00].

2.2.1. Background and Key Safety Data with a Prior Maturation Inhibitor

Bristol-Myers Squibb (BMS), and later ViiV Healthcare (VH), developed a structurally similar HIV-1 MI (BMS-955176/GSK3532795), which was studied through Phase 2b studies in both treatment-naïve (AI468038/205891) and experienced (AI468048/205892) HIV-1 infected adults. In study AI468038/205891, a greater number of participants who received GSK3532795 experienced GI intolerability (most frequently Grade 1 to 2 diarrhea and abdominal pain). A detailed examination of all GI adverse events (AEs) (regardless of grade/relationship) revealed a relationship with dose [GSK Document Number 2016N302783_00]. Ultimately, the rate of GI intolerability in the GSK3532795 dose groups in the Phase 2b study 205891 in part led to VH's decision to end all trials and not progress to Phase 3 studies. Gastrointestinal AEs were also previously observed in healthy participants in Phase 1 studies with varying doses, durations, and formulations of GSK3532795. In both studies, the most common GI AEs were abdominal pain and diarrhea.

Aside from mild to moderate GI intolerability, 2 serious adverse events (SAEs) occurred in the Phase I Thorough QT study AI468044/206220 [BMS Document Control Number 930109388] at supra-therapeutic doses: 1 healthy participant had an episode of acute psychosis and another had suicidal ideation/homicidal ideation as diagnosed through an interview by a psychiatrist. The 2 participants received GSK3532795 240 mg twice daily and 240 mg once daily (QD) with food, respectively. These events were assessed as related to study drug but were not observed in any other clinical study with GSK3532795. The most frequent neuropsychiatric AEs in studies with GSK3532795 were headache, dizziness, and sleep abnormalities (e.g., insomnia, abnormal dreams).

2.2.2. Preliminary Safety and Pharmacokinetic Data in Study 207187

The primary objective of the first time in human (FTIH) clinical trial (207187) was to investigate the safety and tolerability of GSK3640254 following single and repeated daily administration. A total of 78 healthy men were ultimately randomized: 20 in the single-ascending dose (SAD, doses ranging from 1 to 700 mg) and 58 in the multiple-ascending dose (MAD, 50 to 320 mg QD for 14 days). A comprehensive summary of results is described in the CIB [GSK Document Number 2018N379610_00] and the Study Synopsis [GSK Document Number 2018N375461_00]. A concise summary of the data is presented below.

No deaths or SAEs were reported. There were 4 AEs leading to discontinuation. Only 1 of these AEs was related to study medication. A subject who received GSK3640254 200 mg QD developed a maculopapular rash after 8 days of study medication. The rash lasted for 6 days and there were no laboratory abnormalities. A dermatology consultant concluded this was a drug rash and the subject later received fexofenadine 180 mg QD/a topical steroid cream with resolution. The other 3 AEs occurred in SAD portion of the study (depression in a subject who received placebo and 2 subjects with viral infection).

There were 9 subjects with 12 AEs assessed as related to study medication by the principal investigator (11 Grade 1; 1 Grade 2). The most clinically notable was a subject who developed elevated transaminases while receiving GSK3640254 50 mg QD for 14 days. Specifically, there was a progressive rise in alanine aminotransferase (ALT) during treatment with a peak ALT of 83 IU/L on Day 16. The remaining liver chemistries were normal throughout. An ultrasound showed a subcapsular area of heterogenous echogenicity within segment 7, measuring approximately 35 × 23 × 36 mm. Follow-up magnetic resonance imaging and liver chemistries were normal. This subject also had 3 unrelated AEs during the course of an isolated increased ALT: musculoskeletal stiffness, contact dermatitis, and headache. All other related AEs are described in the CIB [GSK Document Number 2018N379610_00] and the Study Synopsis [GSK Document Number 2018N375461_00].

In the SAD portion of the study, 17 subjects experienced 60 individual AEs (58 Grade 1; 2 Grade 2). The 2 Grade 2 AEs were headache and depression (both unrelated). The most frequent AEs were headache, contact dermatitis primarily due to electrocardiogram (ECG) electrodes, and diarrhea. There was no dose/AE relationship.

In the MAD portion of the study, 44 subjects experienced 130 individual AEs (126 Grade 1; 4 Grade 2). The 3 Grade 2 AEs were headache (1 related and 1 unrelated) and back pain (2 unrelated). The most frequent AEs were headache, contact dermatitis, dizziness, contusion, fatigue, and back pain.

There were no clinically significant abnormal fluctuations or trends in vital signs in the SAD or MAD cohorts. There were no abnormal clinically significant arrhythmias or QT prolongations (values >500 ms or increases >60 ms from Baseline) observed for any participant in the SAD or MAD. A cardiodynamic evaluation of healthy subjects in the MAD portion of Study 207187 (placebo or GSK3640254 dose range 50 to 320 mg daily for 14 days) was performed. Serial ECGs were extracted from continuous Holter monitors at time-matched baseline on Day -1 and for approximately 24 hours post-dose

on Days 1 and 14. In the concentration-QTc analysis, a final model with a treatment effect-specific intercept reasonably represented the data. The slope of the concentration-QTc relationship was 0.004 ms per ng/mL (90% confidence interval [CI]: 0.0023 to 0.0048) with a small treatment effect-specific intercept of -0.9 ms (90% CI: -4.47 to 2.69). The QT effect (ΔΔQTcF) of GSK3640254 could be predicted to be 5.38 ms (90% CI: 1.66 to 9.10) and 6.70 ms (90% CI: 2.79 to 10.61) for the 200 mg (1779 ng/mL) and 320 mg (2154 ng/mL) doses, respectively, on Day 14. Based on this concentration-QTc analysis, a QTcF effect above 10 ms could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately ≤200 mg QD; note, the dose used in this study is 200 mg QD). Finally, there were no laboratory abnormality trends across doses that were clinically significant or associated with any symptoms.

Preliminary GSK3640254 PK parameters derived based on nominal sampling times following single doses of 1 to 700 mg administered after a moderate calorie and fat breakfast showed GSK3640254 was slowly absorbed with a median time of maximum observed concentration (Tmax) observed between 3 to 4.5 hours after dosing with a moderate fat breakfast and slowly eliminated with a mean half-life ranging from 22 to 26 hours. In general, exposure (maximum observed concentration [Cmax] and area under the concentration-time curve [AUC]) increased in a close-to-dose-proportional manner from 1 to 400 mg with no further increase in exposure at 700 mg.

Repeat dose preliminary PK parameters following administration of GSK3640254 50 to 320 mg QD for 14 days were determined on Day 1 and Day 14 and showed a median Tmax ranging between 3.8 to 4.3 hours. The mean half-life ranged from approximately 22 to 29 hours. Overall, there was a trend of a slightly less than dose-proportional increase in Cmax and AUC from time 0 to 24 hours after dosing (AUC[0-24]) from 50 to 320 mg. The exposure on Day 14 was, on average, 1.9- to 2.3-fold higher than that of Day 1 for Cmax and 2.2- to 2.6-fold higher than Day 1 for AUC(0-24). Detailed summary statistics are available in the Study Synopsis [GSK Document Number 2018N375461_00].

2.2.3. Preliminary Safety and Pharmacokinetic Data in Study 208131

The FTIH Study 207187 used a bis-hydrochloride salt capsule formulation of GSK3640254, which is not suitable for long term clinical development.

Study 208131 was a single-center, open-label, 2-period, 2-sequence crossover design, conducted in 14 healthy subjects in the United Kingdom. This study was designed to assess the relative bioavailability of the formulation planned for Phase 2a (mesylate salt in a capsule) to the FTIH formulation (bis-hydrochloride salt in a capsule) administered following a moderate calorie and fat meal. All subjects completed dosing and the blinded preliminary safety data showed a total of 11 AEs (all Grade 1). Two AEs of headache were related to study drug. The most common AE was headache (3 instances). There were 3 GI AEs (abdominal pain, bleeding gums, and flatulence). There were no cardiac or psychiatric AEs. There were no clinically significant changes in vital signs, ECG parameters, or safety laboratory parameters.

Preliminary PK results from study 208131 showed that in the presence of a moderate fat meal, the relative bioavailability of GSK3640254 following 200 mg GSK3640254 mesylate salt administration relative to 200 mg GSK3640254 bis-hydrochloride salt administration was 110% and 116% based on AUC from time zero extrapolated to infinity (AUC[0-∞]) and Cmax, respectively.

2.2.4. Ethinyl Estradiol and Levonorgestrel

Portia has been marketed in the United States (US) since 2002 as a combination oral contraceptive. Portia contains 0.03 EE and 0.15 mg LNG. Each blister card provides 21 pink active tablets, and 7 white inert tablets. Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increases the difficulty of sperm entry into the uterus) and endometrium (which reduces the likelihood of implantation). When taken correctly, oral contraceptives have a failure rate of less than 1% per year [Levonorgestrel and Ethinyl Estradiol, 2012].

Portia is administered orally. Both EE and LNG are widely distributed. Ethinyl estradiol is highly protein-bound to albumin and induces an increase in the serum concentrations of both sex hormone-binding globulin (SHBG) and corticosteroid binding globulin. Levonorgestrel is strongly protein-bound, primarily to albumin and SHBG. Steady state is reached in approximately 11 days. Excretion of the oral contraceptive steroids as inactive metabolites occurs via the urine and feces. Elimination half-life is approximately 15 hours for EE and 30 hours for LNG at steady state. It is the prolonged biologic effects of the hormones that allows for once-daily administration [Levonorgestrel and Ethinyl Estradiol, 2012].

2.3. Benefit/Risk Assessment

Based upon preclinical and clinical studies, the major risks for GSK3640254 are GI intolerability (e.g., abdominal pain and diarrhea) and toxicity, prolongation of the corrected QT interval (QTc), and neuropsychiatric safety. Reproduction of preclinical GI toxicity findings (e.g., single-cell parietal cell necrosis) would be unlikely during the limited dosing of GSK3640254 in this study. One preclinical study showed 1 dog with an increased QTc interval when given a single dose of GSK3640254. As described in Section 2.2.2, a cardiodynamic analysis of healthy subjects in Study 207187 was conducted. A final model from the MAD data showed a QT effect (ΔΔQTcF) of GSK3640254 could be predicted to be 5.38 ms (90% CI: 1.66 to 9.10) and 6.70 ms (90% CI: 2.79 to 10.61) for the 200 mg (1779 ng/mL) and 320 mg (2154 ng/mL) doses, respectively, on Day 14. Based on this concentration-QTc analysis, a QTcF effect above 10 ms could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately ≤200 mg QD; note, 200 mg QD is the dose used in this study). Importantly, there were no abnormal clinically significant arrhythmias or QTc prolongations (values >500 ms or increases >60 ms from Baseline) in Study 207187. This study contains specific cardiac exclusion criteria, has ECG monitoring (at Tmax once GSK3640254 attains steady state concentration), and has QTcF based stopping criteria.

Finally, the protocol will exclude potential participants with any significant pre-existing psychiatric condition or positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS assessment will also be administered by a clinician (or qualified designee) during the on-treatment portion of the study.

To ensure the overall safety of participants (including, but not limited to, the risk of GI intolerability, QTc prolongation, and neuropsychiatric safety), this clinical study will include healthy adults who will receive clinical, ECG, and laboratory evaluations during their participation. More detailed information about the known and expected benefits and risks and reasonably expected AEs of GSK3640254 may be found in the CIB [GSK Document Number 2018N379610_00].

The use of oral contraceptives is associated with increased risks of several serious conditions including venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, and stroke), hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. Common side effects include headache, vaginal bleeding, nausea/vomiting, acne, dysmenorrhea, increased weight, mood changes, anxiety/panic attacks, breast pain, and migraines. More detailed information about the known and expected risks and reasonably expected AEs for EE/LNG may be found in the package insert [Levonorgestrel and Ethinyl Estradiol, 2012].

2.3.1. Risk Assessment of GSK3640254

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK3640254		
Cardiovascular (QT prolongation)	Preclinically, GSK3640254 inhibited cardiac hERG/IKr potassium, cardiac SCN5A sodium and L-type calcium channel currents recorded from HEK 293 cells stably transfected with complementary DNA from the ion channels. In a single-dose safety pharmacology study in telemeterized dogs, increases in QT interval (up to 20 ms) occurred primarily in 1 dog given 17 mg/kg. Later, there were no GSK3640254-related effects on electrocardiogram (ECG) parameters in dogs given up to 25 mg/kg/day for 4 weeks. In the first time in human study 207187, no participant exhibited QTc change from baseline >60 ms or QTc >500 ms. As described in Section 2.3, in the concentration-QTc analysis, a QTcF effect above 10 ms could be excluded up to GSK3640254 plasma concentrations of approximately 2000 ng/mL (corresponding to doses approximately ≤200 mg QD).	**Screening**: Protocol exclusion criteria based on screening ECG parameters and cardiac medical history. **On-Treatment**: Participants will have ECG monitoring (at a clinically reasonable frequency) during the course of the study (see SoA, Section 1.3) with QTc stopping criteria (see Section 7.1.2).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal (GI) intolerability and toxicity	Clinical signs indicative of GI intolerability (sporadic vomiting and abnormal feces beginning on Day 1 and continuing throughout the dosing periods) occurred mainly in dogs at ≥1 mg/kg/day. Additionally, toxicity findings of single-cell necrosis of parietal cells and/or chief cells were present in preclinical species. These findings were reversible. Finally, GI intolerability (predominately abdominal pain and diarrhea) was seen with a structurally related compound GSK3532795 which was evaluated through Phase 2b dosing.	**Screening:** Protocol exclusion criterion based on pre-existing GI pathology or baseline GI signs/symptoms. **On-Treatment:** Participants will undergo continuous evaluation for AEs during their participation in the study; there will be individual clinical stopping criteria based upon intensity of treatment-emergent AEs. A GI toxicity evaluation and monitoring plan will be available to guide investigators should GI AEs emerge (See Section 8.2.6).
Neurologic/psychiatric safety	Two psychiatric serious adverse events in previous maturation inhibitor GSK3532795 clinical program (acute psychosis, homicidal/suicidal ideation) were seen at supratherapeutic doses in healthy subjects in the thorough QT (TQT) study. From a neurologic and psychiatric AE summary and pharmacokinetic/pharmacodynamic analysis for GSK3532795 across all studies mild Grade 1 headache and Grade 1 sleep abnormalities were the predominant AEs, with a trend for increasing neurologic and psychiatric AEs with increasing dose (based on TQT and Phase 2b studies). No exposure-response relationship was seen for select neurologic and psychiatric AEs (based on TQT and Phase 2b studies). Central nervous system penetration data for GSK3532795 and GSK3640254 in rats demonstrate a similarly low	**Screening**: Protocol exclusion criterion based on any pre-existing psychiatric condition (including results of psychological assessment) for participants. Participants will have a clinician (or qualified designee) administered Columbia Suicide Severity Rating Scale (C-SSRS) and will be included given no positive (abnormal) response. **On-Treatment:** Participants will undergo physical examinations and laboratory testing. In addition, participants will undergo continuous evaluation for AEs during their participation in the study; there are individual clinical stopping criteria and monitoring based upon incidence and intensity of treatment-emergent psychiatric AEs (Section 7.1.4 and Section 8.2.5). Participants will be housed throughout study conduct to ensure rapid diagnosis and management of any

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	brain distribution/penetration.	potential event. The C-SSRS will be administered during and after the treatment phase of the study. In the event of a positive (abnormal) response confirmed by the investigator, the participant will discontinue from the trial and the investigator will arrange for urgent specialist psychiatric evaluation and management. Guidance for the investigator on the management of emergent psychiatric symptoms will be available.

2.3.2. Benefit Assessment

This is a study in healthy participants; no medical benefit will be derived by volunteers' participation.

2.3.3. Overall Benefit: Risk Conclusion

Given the preclinical profile of GSK3640254, the clinical profile of a structurally similar MI (GSK3532795), the clinical data gathered from Studies 207187 and 208131, and the planned clinical procedures and evaluations in this study, the potential risks to participants receiving GSK3640254 are low, evaluable, and manageable. Given the years of experience with combination contraceptives such as Portia, the potential risks to participants receiving Portia are low, evaluable, and manageable. More detailed information about the known and expected risks and reasonably expected AEs for EE/LNG may be found in the package insert [Levonorgestrel and Ethinyl Estradiol, 2012].

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary • To assess the effect of GSK3640254 on the steady state PK of EE and LNG under fed conditions in healthy female participants	The primary PK endpoints are: • AUC(0-τ), Cmax, and Cτ for EE and LNG
Secondary • To assess the effect of GSK3640254 on the PD of EE/LNG (suppression of ovulation as indicated by endogenous progesterone levels) • To assess the effect of GSK3640254 on LH and FSH • To characterize the steady state PK of GSK3640254 in the presence of EE/LNG • To characterize the steady state PK of EE/LNG alone and in the presence of GSK3640254 • To assess the safety and tolerability of GSK3640254 and EE/LNG when given in combination in healthy female participants	The secondary endpoints are: • Serum progesterone levels • Serum FSH and LH levels • AUC(0-τ), Cmax, Cτ, Tmax, and t1/2 for GSK3640254 • Tmax and t1/2 for EE and LNG • 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 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.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, fixed-sequence, 1-way DDI study designed to assess the PK, PD, safety, and tolerability of GSK3640254 and an oral contraceptive containing EE/LNG (Portia) when administered alone and in combination in healthy female participants.

The study will consist of a screening period, check-in, a run-in period, and a treatment period with Portia given alone and in combination with GSK3640254. Participants will be screened within 28 days before check-in (Day -4). The treatments will be as follows:

- Run-in Period: 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 of the treatment period
- Treatment B: Portia (0.03 mg EE/0.15 mg LNG) QD coadministered with GSK3640254 200 mg on Days 11 to 21 of the treatment period

Participants should take Portia in the morning at approximately the same time throughout study participation.

During the treatment period, participants will fast overnight for at least 8 hours prior to dosing with GSK3640254 and will receive a moderate fat meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption.

Blood samples for the analysis of EE and LNG will be collected before dosing on Days 9 to 10 and 19 to 21, and up to 24 and 72 hours after dosing on Days 10 and 21 of the treatment period, respectively. Blood samples for the analysis of GSK3640254 will be collected before dosing on Days 19 to 21, and up to 96 hours after dosing on Day 21 of the treatment period.

Blood samples for the analysis of progesterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) will be collected on Days 1, 10, 11, 21, and 22 of the treatment period.

Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings.

Study assessments will be performed as indicated in the Schedule of Activities (SoA) (Section 1.3). Participants will check into the clinic on Day -4 and will remain confined until discharge on Day 25. The duration of the study, including Screening and Run-in, is approximately 8 weeks.

4.2. Scientific Rationale for Study Design

This is an open-label, fixed-sequence, 1-way drug interaction study to investigate the effect GSK3640254 has on the PK of a combination oral contraceptive containing EE and LNG.

The inhibitory potential (direct and metabolism-dependent inhibition) of GSK3640254 towards 7 major human hepatic cytochrome P450 (CYP) enzymes was evaluated in human liver microsomes [CIB, GSK Document Number 2018N379610_00]. GSK3640254 demonstrated minimal direct inhibition of all 7 CYP isoforms tested (half maximal inhibitory concentration [IC50] values >13.3 μM). At the maximum projected clinical dose of 200 mg, there is a low risk for clinically meaningful CYP-mediated DDIs with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.

GSK3640254 did not demonstrate human pregnane X receptor or vitamin D receptor mediated transactivation of CYP3A. Therefore, it is unlikely that GSK3640254 would induce CYP3A, or other pregnane X receptor and vitamin D receptor regulated enzymes/transporters in humans. In addition, GSK3640254 was tested in a panel of CYP induction assays using inducible cryopreserved human primary hepatocytes and showed no induction (half maximal effective concentration > 5 μM) of CYP3A4, CYP2B6, and CYP1A2.

GSK3640254 is an inhibitor of organic anion-transporting polypeptide (OATP)1B3 and multi-drug resistance protein (MRP)2 in vitro and has the potential of generating DDIs with substrates of these transporters at the projected human systemic exposures. The IC50 values of GSK3640254 against OATP1B3 and MRP2 were 0.55 and 2.2 μM, respectively. In addition, GSK3640254 was an inhibitor of uridine diphosphate glucuronosyltransferase (UGT)1A1 in vitro (IC50 = 3.9 μM) and clinical DDIs via this mechanism could be possible although literature reports have not revealed clinically significant DDIs with greater than 2-fold change in exposure, with a few exceptions, due to UGT1A1 inhibition [Lin, 2002; Williams, 2004]. A clinically meaningful DDI risk due to UGT1A1 inhibition by GSK3640254 is likely minimal.

Sulfate conjugation accounts for approximately 60% of the first-pass metabolism of EE and once absorbed, hydroxylation by CYP3A4 and glucuronidation occur. GSK3640254 has an unknown impact on sulfotransferases. Ethinyl estradiol is an inhibitor of CYP2C19, CYP3A4, and UGT. There is a risk that GSK3640254 may impact EE exposure due to its effect on UGT and its unknown effect on sulfotransferases. Levonorgestrel and its Phase I metabolites are excreted primarily as glucuronide conjugates. Levonorgestrel is not subject to first pass metabolism and has nearly 100% bioavailability, therefore, there is low likelihood of a DDI at the absorption step.

This study is designed in accordance with the US Food and Drug Administration Guidance for Industry, Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications [DHHS, 2017] to assess the PK, safety, and tolerability of GSK3640254 and EE/LNG when administered alone and in combination.

4.3. Justification for Dose

The dose of 200 mg GSK3640254 was selected for this study as the maximum projected clinically therapeutic dose of GSK3640254 is 200 mg QD. The apparent terminal phase half-life (t1/2) of GSK3640254 was approximately 22 hours in the MAD portion of Study 207187 at the 200-mg dose, and predicted time to steady state is approximately 5 days. The doses of 0.03 mg EE/0.15 mg LNG in Portia are standard, effective doses for an oral contraceptive.

4.4. End of Study Definition

A participant is considered to have completed the study if she has completed all phases of the study including the final date on which data were or are expected to be collected.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 50 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring (history and ECG).

Weight

3. Body weight ≥ 45.0 kg (99 lbs) and body mass index (BMI) within the range 18.5 to 31.0 kg/m^2 (inclusive).

Sex

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

4. Female
    a. Participant must not be pregnant or breastfeeding.
    b. Participant is a woman of childbearing potential (WOCBP) with intact ovarian function, as determined by medical history. Participants must use Portia for the duration of the run-in and treatment periods.
    c. WOCBP must have been on an acceptable form of contraceptive for at least 28 days prior to start of study intervention. Acceptable forms of contraception prior to study intervention include the following:
        - Intrauterine device or intrauterine system
        - Combined estrogen and progestogen oral contraceptive
        - Contraceptive vaginal ring
        - Percutaneous contraceptive patches (if used, the patch must be removed during study participation)
        - Bilateral tubal occlusion
        - Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject. The documentation on male sterility can come from the site personnel’s review of subject’s medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.
        - Sexual abstinence. Note: Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse on a long term and persistent basis when this is their preferred and usual lifestyle. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
    d. Participants who have been on a stable regimen of an oral contraceptive for at least 3 consecutive months must be without evidence of breakthrough bleeding or spotting.
    e. Participants who have been taking oral contraceptives should continue their current regimen until check-in to the clinic for the run-in period. Participants not currently taking an oral contraceptive are eligible, provided all other eligibility criteria are met.
    f. Participants may proceed to the treatment period provided the toxicity profile during the run-in period with Portia is acceptable in the opinion of the investigator.
    g. Participants must agree to use an additional method of contraception from the list of contraceptive methods below for the run-in period, treatment period, and for 28 days after the last dose of study intervention:
        - Non hormonal Intrauterine device
        - Bilateral tubal occlusion

- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.
- Sexual abstinence. Note: Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse on a long term and persistent basis when this is their preferred and usual lifestyle. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
- For the 28 days after study exit, women may resume oral contraceptives but double barrier methods (a combination of male condom with either cervical cap, diaphragm, or sponge with spermicide) must be used in addition.

h. Women of childbearing potential must have a negative highly sensitive serum pregnancy test on Day -4 and Day -1.

i. Additional requirements for pregnancy testing during and after study intervention are outlined in Appendix 3.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 4 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical History

1. History of jaundice associated with taking oral contraceptives or with pregnancy.
2. History of clinically significant irregular bleeding while taking oral contraceptives.
3. History of past deep venous thrombosis, pulmonary embolism, stroke, transient ischemic attack, phlebitis, or migraine headaches with prolonged aura.
4. History of cerebrovascular or coronary artery disease.
5. History of retinal vascular lesions.
6. History of carcinoma of the breast, endometrium, or other known estrogen-dependent neoplasia.
7. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

8. A pre-existing condition interfering with normal GI anatomy or motility (e.g., gastroesophageal reflux disease, gastric ulcers, gastritis), hepatic and/or renal function, that could interfere with the absorption, metabolism, and/or excretion of the study drugs or render the participant unable to take oral study intervention.
9. Any history of significant underlying psychiatric disorder, including, but not limited to, schizophrenia, bipolar disorder with or without psychotic symptoms, other psychotic disorders, or schizotypal (personality) disorder.
10. Any history of major depressive disorder with or without suicidal features, or anxiety disorders that required medical intervention (pharmacologic or not) such as hospitalization or other inpatient treatment and/or chronic (>6 months) outpatient treatment. Participants with other conditions such as adjustment disorder or dysthymia that have required shorter term medical therapy (<6 months) without inpatient treatment and are currently well-controlled clinically or resolved may be considered for entry after discussion and agreement with the VH/GSK Medical Monitor.
11. Any pre-existing physical or other psychiatric condition (including alcohol or drug abuse), which, in the opinion of the investigator (with or without psychiatric evaluation), could interfere with the participant's ability to comply with the dosing schedule and protocol evaluations or which might compromise the safety of the participant.
12. Medical history of cardiac arrhythmias, prior myocardial infarction in the past 3 months, or cardiac disease or a family or personal history of long QT syndrome.

Laboratory Assessments

13. Presence of hepatitis B surface antigen at Screening or within 3 months prior to starting study intervention.
14. Positive hepatitis C antibody test result at Screening or within 3 months prior to starting study intervention AND positive on reflex to hepatitis C RNA.
15. Positive HIV-1 and -2 antigen/antibody immunoassay at Screening.
16. ALT >1.5 × upper limit of normal (ULN). A single repeat of ALT is allowed within a single screening period to determine eligibility.
17. Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
18. Any acute laboratory abnormality at Screening which, in the opinion of the investigator, should preclude participation in the study of an investigational compound.
19. Any Grade 2 to 4 laboratory abnormality at Screening, with the exception of creatine phosphokinase (CPK) and lipid abnormalities (e.g., total cholesterol, triglycerides, etc), and ALT (described above), will exclude a participant from the study unless the investigator can provide a compelling explanation for the laboratory result(s) and has the assent of the sponsor. A single repeat of any laboratory abnormality is allowed within a single screening period to determine eligibility.

20. A positive test result for drugs of abuse (including marijuana), alcohol, or cotinine (indicating active current smoking) at Screening or before the first dose of study intervention.

Prior/Concomitant Therapy

21. Unable to refrain from the use of prescription or nonprescription drugs including vitamins, herbal and dietary supplements (including St John's wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study intervention and for the duration of the study. (Note: acetaminophen/paracetamol at doses of ≤2 grams/day and hydrocortisone cream 1% are permitted for use any time during the study.)
22. Treatment with any vaccine within 30 days prior to receiving study intervention.
23. Unwillingness to abstain from excessive consumption of any food or drink containing grapefruit and grapefruit juice, Seville oranges, blood oranges, or pomelos or their fruit juices within 7 days prior to the first dose of study intervention(s) until the end of the study.

Prior/Concurrent Clinical Study Experience

24. Participation in another concurrent clinical study or prior clinical study (with the exception of imaging trials) prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
25. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.

Diagnostic assessments

26. Any positive (abnormal) response confirmed by the investigator on a screening clinician- or qualified designee-administered C-SSRS.
27. Any significant arrhythmia or ECG finding (e.g., symptomatic bradycardia, nonsustained or sustained atrial arrhythmias, nonsustained or sustained ventricular tachycardia, second-degree atrioventricular block Mobitz Type II, or third-degree atrioventricular block) which, in the opinion of the investigator or VH/GSK Medical Monitor, will interfere with the safety for the individual participant.
28. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

Heart rate[1]	<50 or >100 beats per minute
QTcF interval[2] (Fridericia's)	>450 ms

1 A heart rate from 100 to 110 beats per minute can be rechecked by ECG or vital signs within 30 minutes to verify eligibility.

2 The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF). It is either machine read or manually over-read. The specific formula used to determine eligibility and discontinuation for an individual participant in this study will be Fridericia's formula.

Other Exclusions

29. History of regular alcohol consumption within 6 months of the study defined as: an average weekly intake of >14 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
30. Unable to refrain from tobacco- or nicotine-containing within 3 months prior to screening.
31. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from excessive consumption of red wine, grapefruit and grapefruit juice, Seville oranges, blood oranges, or pomelos or their fruit juices within 7 days prior to the first dose of study intervention(s) until the end of the study. Excessive consumption is defined as more than one glass of wine or juice or one of these fruits per day, in combination.
- Unless otherwise indicated, all doses of GSK3640254 in this study will be administered in the fed state. The participants will fast overnight for at least 8 hours prior to dosing and will receive a moderate fat meal 30 minutes prior to dosing. Participants will eat this meal in 30 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours post-dose on serial PK sampling days (Days 10 and 21 of the treatment period). The moderate fat meal will contain about 600 calories with approximately 30% of the calories coming from fat.
- No water is allowed from 1 hours prior to dosing until 1 hours after dosing with GSK3640254 except for the glass of water needed to administer the study intervention (e.g., 240 mL). Water is allowed ad libitum at all other times.
- A standard lunch will be provided 4 hours after dosing with GSK3640254. A standard dinner will be served approximately 10 hours after dosing. The food content of meals must be identical on serial PK sampling days (e.g., Days 10 and 21 of the treatment period).

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK sample.
- Participants will abstain from alcohol for 48 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco and nicotine-containing products will not be allowed from 3 months prior to Screening until after the final visit.

- Participants must have a negative drug test at Screening and check-in on Day -4 and must abstain from recreational drug use from Screening until after the final visit.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

Intervention Name	GSK3640254	Portia
Type	drug	drug
Dose Formulation	capsule	tablet
Unit Dose Strength(s)	100 mg	0.03 mg ethinyl estradiol 0.15 mg levonorgestrel
Dosage Level(s)	200 mg once daily	0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel once daily
Route of Administration	oral	oral
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided locally by the trial site
Packaging and Labeling	Study Intervention will be provided in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in blister cards. Each blister card will be labeled as required per country requirement.

IMP = investigational medicinal product; NIMP = noninvestigational medicinal product

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual (SRM).
5. Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
6. A Material Safety Data Sheet/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from VH/GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. All participants will receive the same treatment.

6.4. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Acetaminophen/paracetamol at doses of ≤2 grams/day and hydrocortisone cream 1% are permitted for use any time during the study and their use should be documented in the case report form (CRF). Other medications are not permitted without prior discussion with the VH/GSK medical monitor.

6.6. Dose Modification

Not applicable.

6.7. Intervention after the End of the Study

Participants will not receive any additional treatment from VH/GSK, or with GSK3640254, after the completion of the study because only healthy volunteers are eligible for study participation.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention.

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration premarketing clinical liver safety guidance: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf).

Discontinuation of study intervention for abnormal liver tests is required when a participant has an ALT ≥3 × ULN or if the investigator believes study intervention discontinuation is in the best interest of the participant.

Details of liver safety follow-up procedures are described in Appendix 5.

7.1.1.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.1.2. QTc Stopping Criteria

The *same* Fridericia QT correction formula (QTcF) *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

- The Baseline QTcF should be based on averaged QTcF values of triplicate ECGs obtained over a brief (e.g., 5 to 10 minute) recording period from the Day -4 ECG.
- A randomized participant that develops an on-treatment QTcF >500 ms or an increase from baseline QTcF >60 ms should have two repeat unscheduled ECGs within 10 minutes. Using these triplicate ECGs, if the average QTcF >500 ms or an increase from baseline QTcF >60 ms, the participant will be withdrawn from the study. Finally, this participant should have repeated unscheduled ECGs until their QTcF measurement returns to their original averaged QTcF value at Day -4.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.3. Columbia Suicide Severity Rating Scale Criteria

Emergence of any positive (abnormal) response confirmed by the investigator on a clinician (or qualified designee) administered C-SSRS during the on-treatment phase of the study will be cause for discontinuation of study intervention.

Refer to the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.4. Individual Participant Laboratory Abnormality and Adverse Event Stopping Criteria

Investigators should make every effort to have a discussion with the medical monitor before the next dose to help assess if the study intervention should be stopped.

- Any clinically significant AE deemed to require discontinuation of study intervention
- Any Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement
- Any allergic or hypersensitivity reactions to either or both drugs
- Any Grade 3 or higher psychiatric AE
- New onset suicidal ideation
- Any Grade 3 or higher AE related to study intervention
- Any Grade 4 AE or laboratory abnormalities (with the exception of an asymptomatic Grade 4 cholesterol, triglyceride, or CPK increase)

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who is withdrawn from the study for any reason related to safety (listed in Section 7.1.4 or otherwise) will be continued to be followed to assess the outcome of the safety event that triggered discontinuation of study drug.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 4.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A full physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the semi-recumbent position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 3 blood pressure and pulse measurements (3 consecutive blood pressure and pulse readings will be recorded at intervals of at least 1 minute). Each measurement will be recorded in the CRF. Triplicate vital signs are required only when they occur at the same time point as clinical safety laboratory assessments. Vital signs will be taken as a single measurement at all other time points.

8.2.3. Electrocardiograms

- On Day -4, triplicate ECGs will be taken. The ECGs should be recorded over a brief (e.g., 5 to 10 minute) recording period. Each measurement will be recorded in the CRF.
- Single 12-lead ECG will be obtained at other time points as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.2 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.
- Twelve-lead ECGs will be performed with the participant in a supine or semi-supine position after a rest of at least 10 minutes.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more

than 2 minutes apart. The full set of triplicates should be completed over a brief (e.g., 5 to 10 minute) recording period.

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention should be repeated until the values return to normal or Baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

GSK3640254 is not a central nervous system active drug nor is it being developed for a neurologic or psychiatric condition. However, given the risk of suicidal ideation identified with previous MI GSK3532795, all participants will undergo screening using the C-SSRS administered by a clinician (or qualified designee); any positive (abnormal) response confirmed by the investigator, will exclude them from participating. A repeat assessment will be done at Day 11 and at the end of the treatment phase of the study. In case of positive (abnormal) response confirmed by the investigator, the participant will discontinue from the trial and the investigator will arrange for urgent specialist psychiatric evaluation and management.

As described in Section 7.1.4, new onset suicidal ideation at any time will result in immediate discontinuation from the trial and the investigator will arrange for urgent specialist psychiatric evaluation and management.

The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment.

Emergent non-suicidal psychiatric AE Evaluation and Management:

- Any Grade 1 or 2 psychiatric AE: A Grade 1 or 2 psychiatric AE may result in additional unscheduled visits (in-clinic or at home) as clinically indicated. This may include a more in-depth assessment of AE through interview, additional unscheduled clinical laboratory samples, and/or imaging. Psychiatric consultation may be required at the discretion of the investigator. Any pharmacotherapy should be discussed with the medical monitor.

- Any Grade 3 or 4 psychiatric AE: As described in Section 7.1.4, a Grade 3 or 4 psychiatric AE will result in discontinuation from the trial and emergency psychiatric evaluation (including potential hospitalization and pharmacotherapy as indicated).

8.2.6. Gastrointestinal Toxicity Evaluation and Monitoring Plan

Preclinical toxicology studies in rats and dogs have suggested a potential for GI-related toxicity with GSK3640254. This section provides general guidance to the investigator on the evaluation and management of primarily upper GI symptoms (Table 1). The investigator may contact the VH/GSK Medical Monitor to discuss evaluation and management (including discontinuation of a participant) of any GI symptoms throughout the study.

Table 1 Gastrointestinal Toxicity Evaluation and Management

HISTORY	**For symptoms of all grades, a thorough history forms the foundation of proper evaluation and management. The following are potential manifestations of some GI clinical syndromes that may occur (possibly in combination) during the clinical study.**
Nausea and Vomiting	The investigator should attempt to identify the etiology of these symptoms (and whether it is intraperitoneal, extraperitoneal, medication related, infection related, or due to a metabolic disorder [Hasler, 2012]. Medications can cause nausea and vomiting acutely.
Dyspepsia	The investigator should identify the presence of red flags (odynophagia, unexplained weight loss, recurrent vomiting, GI bleeding, jaundice, palpable mass or adenopathy, or family history of GI malignancy). Symptoms of dyspepsia could include early satiety, bloating, or belching. Additionally, atypical symptoms of dyspepsia could include: pharyngitis, asthma, bronchitis, hoarseness, chest pain, or abdominal pain.
Other Clinical Syndromes	Additional diagnostic criteria for other GI disorders potentially encountered in the clinical study are available elsewhere [Rome Foundation, 2018].

PHYSICAL EXAMINATION	**Physical examination should complement elements obtained from the history [Hasler, 2012]. Acutely, the investigator may assess for signs of intravascular volume depletion (e.g., orthostasis) and/or aspiration of vomitus as appropriate. Abdominal tenderness and guarding may indicate inflammation. The presence of fecal blood can indicate mucosal damage (e.g., from an ulcer). Complete evaluation of dyspepsia should include an oral examination (poor dentition or pharyngeal erythema) and lungs for wheezing.**
DIAGNOSTIC EVALUATION AND MANAGEMENT	**A major goal in the diagnostic evaluation of a participant with upper GI symptoms is to quickly arrive at a final diagnosis without exposing the participant to unnecessary (invasive) testing; investigators should exercise good clinical judgment in this regard [Soll, 2009]. A major goal of therapy is directed at correcting the underlying identifiable medical or surgical abnormalities. Consultation (e.g., gastroenterologist) is recommended as clinically indicated.**
Grade 1 symptoms	Participants may be treated symptomatically. If participants develop dyspepsia alone, generally only limited and direct diagnostic testing should be performed. If the participant has dyspepsia they should limit alcohol, caffeine, chocolate, tobacco, and eating directly before bedtime.
Grade 2 symptoms	Diagnostic testing may include but is not limited to the following (as clinically indicated): • Serum chemistries and assessment of hemoglobin if not recently performed • Testing for *Helicobacter pylori* • Polymerase chain reaction for viruses (e.g., cytomegalovirus) For participants who are infected with *H. pylori*, discontinuation from the study is necessary. Management should be targeted at addressing the underlying pathology.
Grade 3 symptoms [1]	Diagnostic testing may include but is not limited to the following (as clinically indicated): • The testing outlined above in Grade 2 • A barium swallow • Computed tomography scan to identify GI inflammation • Upper endoscopy with biopsy as indicated (e.g., mucosal injury or the presence of red flags) Management should be targeted at addressing the underlying pathology.
Grade 4 symptoms [1]	Diagnostic testing may include but is not limited to the following (as clinically indicated): • The testing outlined above in Grade 2 and Grade 3 • An acute abdominal series Initial management can include correction of hemodynamic and electrolyte abnormalities as clinically indicated. After stabilization, management should be targeted at addressing the underlying pathology.

GI = gastrointestinal.

1 A Grade 4 or related Grade 3 AE: The Investigator will discontinue the participant from the study and perform an evaluation/management plan incorporating elements described above.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 6. As described in Appendix 6, intensity of AEs (and laboratory abnormalities) will be graded using the most recent version of the Division of AIDS (DAIDS) grading table at the time of the last participant last visit. While the study population will consist of HIV-1 seronegative healthy volunteers, the DAIDS criteria will be used in later phase clinical studies (Phase 2a and beyond); additionally, the DAIDS criteria have a more conservative grading scale relative to other scales (eg. CTCAE v 4.0). Thus, participant safety evaluation and monitoring will be more conservative.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE, and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the ICF until the end of the study at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of intervention until the end of the study at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 6. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- The methods of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 6.
- Care will be taken not to introduce bias when detecting an AE and/or SAE. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 6.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the CIB and will notify the IRB/IEC, if appropriate, according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention through the end of pregnancy (termination or delivery).
- The investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study and up to 38 days post-treatment completion.
- If a pregnancy is reported, the investigator should inform VH/GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4. Treatment of Overdose

For this study, any dose of GSK3640254 or Portia greater than the planned dose within a 24-hour time period (±2 hours) will be considered an overdose.

VH/GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3640254 can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis immediately and through 7 days after the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK3640254 as specified in the SoA (Section 1.3).
- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of EE, and 2 mL will be collected for LNG (i.e., total of 4 mL for the 2 analytes) as specified in the SoA (Section 1.3).
- A maximum of 10 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of GSK3640254, EE, and LNG. Samples collected for analyses of GSK3640254, EE, and LNG plasma concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.
- Once the plasma has been analyzed for GSK3640254, EE, and LNG, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

8.6. Pharmacodynamics

Venous blood samples of approximately 3.5 mL will be collected for measurement of serum progesterone, FSH, and LH at the time points indicated in the SoA (Section 1.3).

8.7. Genetics

A 6-mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 7 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. 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.

9.2. Sample Size Determination

The historical references used for to calculate the intrasubject coefficient of variability (CVw) for PK parameters of EE and LNG are provided in Table 2.

Table 2 Intrasubject Coefficient of Variability for PK Parameters of EE and LNG

Historical Reference	Analyte	Parameter	n	CVw%
Anderson, 2011	EE	AUC(0-τ)	19	9.9
		Cmax	19	13.4
Barr Laboratories, 2000	EE	AUC(0-τ)	30	13.2
		Cmax	30	13.7
	LNG	AUC(0-τ)	30	16.6
		Cmax	30	13.5
Butler, 2011	EE	AUC(0-τ)	22	30.2
		Cmax	22	19.3
	LNG	AUC(0-τ)	22	12.1
		Cmax	22	12.4
Sevinsky, 2011	EE	AUC(0-τ)	21	22.1
		Cmax	21	21.3
	LNG	AUC(0-τ)	6	19.7
		Cmax	6	12.3
Trezza, 2017	EE	AUC(0-τ)	17	8.9
		Cmax	19	19.3
	LNG	AUC(0-τ)	19	8.7
		Cmax	19	16.1

Based upon the historical references [Anderson, 2011; Barr Laboratories, 2000; Butler, 2011; Sevinsky, 2011; Trezza, 2017] a weighted average was obtained as 17.1%, 17.2%, 13.6%, 13.7% for EE AUC(0-τ), EE Cmax, LNG AUC(0-τ), and LNG Cmax, respectively. The largest weighted average CVw for the analytes and parameters was 17.2%.

The power computation was performed using PASS 15.0.7 procedure for "Equivalence Tests for the Ratio of Two Means in a 2×2 Cross-Over Design": a CVw of 17.2%, Type I error of 0.05, true ratio for the means of 0.95, and a required statistical power of 90%. The number of evaluable participants required is 19 to achieve at least 90% statistical power. For ease of implementation, a total of 25 participants will be enrolled to ensure at least 20 provide evaluable data in both test and reference periods.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who sign the ICF.
Safety	All participants who receive at least 1 dose of study medication. This population will be used for all demographic and safety summaries.
Pharmacokinetic Concentration	The PK Concentration Population will include all participants who undergo plasma PK sampling and have evaluable PK assay results. This population will be used for the concentration listing.
Pharmacokinetic Parameter	The PK Parameter Population will include all participants who undergo plasma PK sampling and have evaluable PK parameters estimated. This population will be used for PK parameter listing, summary tables, and plotting of the concentration-time data and PK parameter summary.
Pharmacodynamic Concentration	The PD Concentration Population will include all participants who undergo plasma PD sampling and have evaluable PD assay results. This population will be used for the concentration listing.

9.4. Statistical Analyses

9.4.1. Pharmacokinetic and Pharmacodynamic Analyses

Plasma EE, LNG, and GSK3640254 concentration-time data will be analyzed by PPD, under the oversight of the Clinical Pharmacology Modeling & Simulation department within GSK, using noncompartmental methods with Phoenix WinNonlin Version 6.4 or higher. Statistical analysis will be performed by PPD, under the oversight of Clinical Statistics, GSK. Calculations will be based on the actual sampling times recorded during the study.

Endpoint	Statistical Analysis Methods

Primary	• The primary endpoints of this study are PK-related. The analysis for the primary PK endpoints will be performed for the PK Parameter Population. Plasma concentrations of EE, LNG, and GSK3640254 will be subjected to PK analyses using noncompartmental methods.
	• Based on the individual concentration-time data the following primary plasma parameters will be estimated:
	  • EE (Treatments A and B): AUC(0-τ), Cmax, and Cτ
	  • LNG (Treatments A and B): AUC(0-τ), Cmax, and Cτ
	• Analyses will be performed to assess the effect of GSK3640254 on the steady state PK of EE and LNG, as appropriate. 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 and subject as a random effect. Effects will be estimated, and CIs will be constructed for the following treatment comparison:
	  • 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.
	• Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma EE and LNG PK parameter values will be summarized by treatment.

Secondary	• Plasma concentrations of GSK3640254 will be subjected to PK analyses using noncompartmental methods.
	• Based on the individual concentration-actual time data the following secondary plasma parameters will be estimated:
	  • EE and LNG (Treatment A and B): Tmax and t1/2 (as data permit)
	  • GSK3640254 (Treatment B): AUC(0-τ), Cmax, Cτ, Tmax, and t1/2 (note: GSK3640254 PK parameter values in the presence of Portia from this study will be compared with GSK3640254 PK parameter values from previous studies)
	• Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma EE, LNG, and GSK3640254 PK parameter values will be summarized by treatment.
	• Additionally, predose (trough) PK plasma concentrations (EE and LNG: Days 9, 10, 11 [Treatment A], 19 through 21 [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.
	• Summary statistics (arithmetic mean, median, standard deviation, minimum, maximum, and coefficient of variation) for serum progesterone, FSH, and LH levels will be summarized by treatment using the PD Concentration Population. Additional data displays will be described in the reporting and analysis plan.

Exploratory	Will be described in the reporting and analysis plan.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library standards. No formal statistical analysis of the safety data will be conducted.

The details of the statistical analyses of safety and PK data will be provided in the reporting and analysis plan.

9.4.3. Other Analyses

Not applicable.

9.5. Interim Analyses

There will be no interim analysis performed.

9.5.1. Data Monitoring Committee (DMC)

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC(0-24)	Area under the plasma concentration-time curve from time 0 to 24 hours after dosing
AUC(0-∞)	Area under the concentration-time curve from time zero extrapolated to infinity
AUC(0-τ)	Area under the plasma concentration-time curve from time 0 to the end of the dosing interval at steady state
BMS	Bristol-Myers Squibb
CFR	Code of Federal Regulations
CI	Confidence interval
CIB	Clinical Investigator's Brochure
Cmax	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
Cτ	Plasma concentration at the end of the dosing interval
CVw	Intra-subject coefficient of variability
CYP	Cytochrome P450
DAIDS	Division of AIDS
DDI	Drug-drug interaction
ECG	Electrocardiogram
EE	Ethinyl estradiol
FSH	Follicle-stimulating hormone
FTIH	First time in human
GCP	Good Clinical Practice
GI	Gastrointestinal
GSK	GlaxoSmithKline
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus

IC50	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
INR	International normalized ratio
IRB	Institutional Review Board
LH	Luteinizing hormone
LNG	Levonorgestrel
MAD	Multiple-ascending dose
MI	Maturation inhibitor
OATP	Organic anion-transporting polypeptide
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QD	Once daily
QTc	Corrected QT interval
QTcF	Fridericia QT correction formula
SAD	Single-ascending dose
SAE	Serious adverse event
SHBG	Sex hormone-binding globulin
SoA	Schedule of activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
t1/2	Apparent terminal phase half-life
Tmax	Time of maximum observed concentration
TQT	Thorough QT
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
USA	United States of America
VH	ViiV Healthcare
WOCBP	Women of childbearing potential

Trademark Information

Trademarks of ViiV Healthcare
NONE

Trademarks not owned by the ViiV Healthcare
Phoenix
Portia
WinNonlin

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the time points indicated in the SoA (Section 1.3).
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count Red Blood Cell Count Hemoglobin Hematocrit	Red Blood Cell Indices: Mean corpuscular volume Mean corpuscular hemoglobin	White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry [1]	Blood urea nitrogen Creatinine Glucose (fasting) Potassium Sodium Calcium Chloride Phosphorus	Carbon dioxide Aspartate aminotransferase Alanine aminotransferase Gamma-glutamyl transferase Total and direct bilirubin Lactate dehydrogenase Total cholesterol Triglycerides	Total protein Albumin Globulin Anion gap Alkaline phosphatase Uric acid Creatine phosphokinase Serum lipase Serum amylase
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase by dipstick • Microscopic examination (if blood, leukocyte esterase, or protein is abnormal)		

Laboratory Assessments	**Parameters**
Other Screening Tests	• Serology: HIV-1 and -2 antigen/antibody immunoassay, hepatitis B surface antigen, hepatitis C antibody • Alcohol, cotinine, and drug screen (to include at minimum amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Pregnancy [2]

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 5. All events of ALT ≥3 ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

10.3.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - Documented bilateral tubal ligation

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>40 IU/L or mIU/mL) is required.

10.3.2. Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
1. Participants who have been taking oral contraceptives prior to study entry should continue their current regimen until check-in to the clinic for the run-in period. 2. Participants must use Portia for the duration of the run-in and treatment periods. 3. Participants must agree to use an additional method of contraception from the list of contraceptive methods below for the run-in period, treatment period, and for 28 days after the last dose of study intervention: • Non hormonal Intrauterine device • Bilateral tubal occlusion • Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner. • Sexual abstinence. Note: Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse on a long term and persistent basis when this is their preferred and usual lifestyle. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. • For the 28 days after study exit, women may resume oral contraceptives but double barrier methods (a combination of male condom with either cervical cap, diaphragm, or sponge with spermicide) must be used in addition.

10.3.3. Collection of Pregnancy Information:

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to VH/GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to VH/GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to VH/GSK as described in Appendix 6. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study intervention or be withdrawn from the study.

10.4. Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

10.4.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, CIB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.4.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.4.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of

informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

10.4.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.4.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a VH/GSK site or other mutually-agreeable location.
- VH/GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with VH/GSK Policy.

10.4.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.4.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the

discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data can be found in the SRM.

10.4.8. Study and Site Closure

VH/GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of VH/GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥3 × ULN
If ALT≥3 × ULN AND bilirubin[1,2] ≥2 × ULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
MONITORING:
If ALT ≥3 × ULN AND bilirubin ≥2 × ULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline
• A specialist or hepatology consultation is recommended</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for PK analysis, obtained within 48 hours of last dose[4]
• Serum CPK and lactate dehydrogenase.
• Fractionate bilirubin, if total bilirubin ≥2 × ULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form</td></tr>
<tr><td>If ALT ≥3 × ULN AND bilirubin <2 × ULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and</td><td colspan="2">If ALT ≥3 × ULN AND bilirubin ≥2 × ULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney</td></tr>
</table>

perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that subject if ALT ≥3 × ULN and bilirubin ≥ 2 × ULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, which may indicate severe liver injury (possible "Hy's Law"), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to subjects receiving anticoagulants.
3. Includes: Hepatitis A immunoglobulin (IgM) antibody, Hepatitis B surface antigen, and Hepatitis B Core Antibody; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

10.6. Appendix 6: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.6.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected DDI. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.6.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.6.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to VH/GSK in lieu of completion of the GSK AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by VH/GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to VH/GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study using the DAIDS grading table Version 2.1, July 2017 (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf) and assign it to 1 of the following categories:

- Mild: no or minimal interference with usual social & functional activities
- Moderate: greater than minimal interference with usual social and functional activities
- Severe: inability to perform usual social and functional activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

- Life Threatening: inability to perform basic self-care functions

  An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the CIB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to VH/GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by VH/GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide VH/GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to VH/GSK within 24 hours of receipt of the information.

10.6.4. Reporting of SAE to VH/GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to VH/GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the electronic CRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to study intervention/study participation (causality) within 72 hours of SAE entry into the electronic CRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to VH/GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SRM.

10.7. Appendix 7: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity, and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to GSK3640254 or HIV and related diseases. They may also be used to develop tests/assays including diagnostic tests related to GSK3640254 or HIV MIs and HIV. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK3640254 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3640254 (or study interventions of this class) or HIV continues but no longer than 15 years after the last participant's last visit or other period as per local requirements.

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