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ORIGINAL ARTICLE

Lack of pharmacokinetic interaction between the HIV-1 maturation inhibitor GSK3640254 and combination oral contraceptives in healthy women

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Aims: GSK3640254 is a next-generation maturation inhibitor likely to be coadministered with combined oral contraceptives in HIV-positive women.

Methods: This phase I, open-label, 1-way study assessed pharmacokinetic and pharmacodynamic interactions of GSK3640254 200 mg and ethinyl oestradiol 0.03 mg/levonorgestrel 0.15 mg once daily in healthy female participants who received ethinyl oestradiol/levonorgestrel for 10 days with a moderate-fat meal after which GSK3640254 was added from Days 11 to 21. Primary endpoints were area under the plasma concentration–time curve to the end of the dosing interval ($AUC_{0\text{-}t}$), maximum observed concentration (C_{max}) and plasma concentration at the end of the dosing interval (C_{τ}) for ethinyl oestradiol and levonorgestrel. Serum follicle-stimulating hormone, luteinizing hormone and progesterone concentrations were determined. Adverse events were monitored.

Results: Among 23 enrolled participants, 17 completed the study. Geometric least squares mean ratios (with *vs*. without GSK3640254) of $AUC_{0\text{-}t}$, C_{max} and C_{τ} were 0.974, 0.970 and 1.050 for ethinyl oestradiol and 1.069, 1.032 and 1.083 for levonorgestrel, respectively. Three participants had elevated progesterone levels, which occurred before GSK3640254 administration in 2 participants. No participants had elevated follicle-stimulating hormone or luteinizing hormone values. Fourteen participants (61%) reported adverse events. Four participants reported asymptomatic elevated transaminase levels meeting liver-stopping criteria; of these, 3 events occurred before GSK3640254 administration and led to study withdrawal.

Conclusion: Ethinyl oestradiol/levonorgestrel plus GSK3640254 coadministration did not affect steady-state pharmacokinetics or pharmacodynamics of ethinyl oestradiol

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The authors confirm that the Principal Investigator for this paper is Theresa T. Pham and that she had direct clinical responsibility for participants.

and levonorgestrel in healthy female participants. No major tolerability findings were reported. Elevated liver transaminase levels were probably due to ethinyl oestradiol/levonorgestrel.

KEYWORDS
drug–drug interaction, ethinyl oestradiol, HIV infection, levonorgestrel, pharmacodynamics

1 | INTRODUCTION

Current combination antiretroviral therapy (ART) regimens for HIV infection primarily target the reverse transcriptase, protease or integrase virus proteins.[1] Despite advances in ART, drug resistance and intolerability may occur, and need exists for novel ART for people living with HIV infection.[1,2]

Maturation is the last step in the HIV life cycle and refers to the processing cascade directed by the viral protease, wherein HIV-1 structural protein (Gag) precursors are cleaved into mature Gag proteins.[3] These cleavage events trigger structural rearrangement in the newly released HIV particles, allowing them to become mature, infectious virions. Given that disruption of HIV-1 maturation results in noninfectious virus particles, viral maturation is a promising target for therapeutic intervention. Novel therapeutic agents, termed maturation inhibitors, block the protease-mediated cleavage of capsid-spacer protein 1 in the Gag polyprotein. In vitro analyses and results from phase I/II clinical studies suggest that pharmacological inhibition of maturation may inhibit replication of HIV-1 isolates.[2,4–8]

GSK3640254 is a next-generation maturation inhibitor that demonstrates inhibition across HIV-1 subtypes and has a preclinical profile that supports its clinical evaluation for HIV-1 ART.[9] Because HIV-1 infection requires lifelong therapy,[1] GSK3640254 is expected to be coadministered with common medications, including combined oral contraceptives.[10] Combined oral contraceptives contain synthetic oestrogenic and progestin hormones, including **ethinyl oestradiol** and **levonorgestrel**, respectively, that inhibit ovulation by suppressing the release of **follicle-stimulating hormone** (FSH) and **luteinizing hormone** (LH).[11] Because decreased ethinyl oestradiol and levonorgestrel concentrations may reduce the efficacy of combined oral contraceptives, it is critical to characterize potential drug interactions when these medications are given in combination with novel or emerging therapies such as GSK3640254.

GSK3640254 is a mild inhibitor of **uridine diphosphate glucuronosyltransferase 1A1** in vitro (half maximal inhibitory concentration, 3.9 μM) and has an unknown impact on sulfotransferases, both of which are enzymes that metabolize ethinyl oestradiol. Whether coadministration of GSK3640254 with a combined oral contraceptive will impact ethinyl oestradiol exposure is unclear, although it is considered to be unlikely. Because levonorgestrel has nearly 100% bioavailability, coadministration of GSK3640254 with a combined oral contraceptive is unlikely to impact levonorgestrel exposure. Herein we report the pharmacokinetics, pharmacodynamics and tolerability of GSK3640254 coadministered with a combined oral contraceptive containing ethinyl oestradiol/levonorgestrel.

What is already known about this subject

- Maturation inhibitors are novel therapeutic agents for HIV-1 infection that disrupt the HIV-1 life cycle by inhibiting HIV-1 maturation.
- The next-generation maturation inhibitor GSK3640254 demonstrates inhibition across HIV-1 subtypes,
- GSK3640254 is expected to be coadministered with combined oral contraceptives in HIV-positive women,

What this study adds

- GSK3640254 did not affect pharmacokinetics or pharmacodynamic interactions of ethinyl oestradiol and levonorgestrel when coadministered with a combined oral contraceptive containing ethinyl oestradiol/levonorgestrel in healthy women.
- These results suggest that coadministration of GSK3640254 and combined oral contraceptives was well tolerated and suitable for combination use in HIV-1 therapy.

2 | METHODS

2.1 | Study design

This was a phase I, open-label, fixed-sequence, 1-way drug interaction study to evaluate the pharmacokinetics, safety, pharmacodynamics and tolerability of a combination oral contraceptive containing ethinyl oestradiol/levonorgestrel when administered alone and in combination with GSK3640254 in healthy women (ClinicalTrials.gov identifier: NCT03984825). The study consisted of a 28-day screening period before check-in (Day −4) and a run-in period (Days −3 to −1) during which participants received ethinyl oestradiol 0.03 mg/levonorgestrel 0.15 mg once daily (QD) before 2 sequential treatment periods. Participants received ethinyl oestradiol 0.03 mg/levonorgestrel 0.15 mg QD on Days 1 to 10, then received ethinyl oestradiol

0.03 mg/levonorgestrel 0.15 mg and GSK3640254 200 mg QD on Days 11–21. Participants fasted overnight for ≥8 hours and consumed a moderate-fat meal 30 minutes before dosing with either ethinyl oestradiol/levonorgestrel or ethinyl oestradiol/levonorgestrel plus GSK3640254; this dosing occurred within 5 minutes of meal consumption at approximately the same time each morning.

The study was designed and conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice following the principles of the Declaration of Helsinki. IntegReview IRB (Austin, TX, USA) approved the study protocol and conduct.

2.2 | Study participants

Eligible study participants were healthy women of childbearing potential with intact ovarian function aged 18–50 years with a body weight of ≥45 kg and a body mass index between 18.5 and 31.0 kg m^{-2}. Eligible participants must have been taking an acceptable form of contraception, which did not need to be hormonal, for ≥28 days before the start of the study, could not be pregnant or breastfeeding, and must have had a negative serum pregnancy test on Days −4 and −1. Acceptable forms of contraception included intrauterine device or system; combined oestrogen and progestogen oral contraceptive; contraceptive vaginal ring; percutaneous contraceptive patches; bilateral tubal occlusion; male partner sterilization with documented azoospermia before study entry; and sexual abstinence. Participants with a history of oral contraceptive use that resulted in either jaundice or clinically significant irregular bleeding were excluded. Other exclusion criteria were related to medical history (e.g., history of cardiovascular, hepatic, gastrointestinal or psychiatric disorders) or certain laboratory assessments, including positive test results for HIV, hepatitis B or hepatitis C; alanine aminotransferase (ALT) levels >1.5× upper limit of normal (ULN); total bilirubin levels >1.5× ULN or isolated bilirubin levels >1.5× ULN and direct bilirubin levels >35%; or any grade 2–4 laboratory abnormality at screening, except for creatine phosphokinase or lipids. Participants were excluded if they received prior or concomitant prescription or over-the-counter medication that could impact the pharmacokinetics of the investigational drug or received a vaccine within 30 days. Other exclusion criteria included a history of alcohol or tobacco use and sensitivity to any study medication. All participants provided written informed consent and could withdraw from the study at any time.

2.3 | Study assessments

The primary endpoint was area under the plasma concentration-time curve from time zero to the end of the dosing interval at steady state ($AUC_{0\text{-}t}$), maximum observed concentration (C_{max}) and plasma concentration at the end of the dosing interval (C_τ) for ethinyl oestradiol and levonorgestrel. Secondary pharmacokinetic endpoints were $AUC_{0\text{-}t}$, C_{max} and C_τ for GSK3640254 and time to C_{max} (t_{max}) and apparent terminal phase half-life ($t_{1/2}$) for ethinyl oestradiol, levonorgestrel and GSK3640254. Additional secondary endpoints included serum FSH, LH and progesterone levels for pharmacodynamics and safety and tolerability parameters.

Blood samples for analysis of ethinyl oestradiol and levonorgestrel were collected before dosing on Days 9, 10 and 19–21 and up to 24 and 72 hours after dosing on Days 10 and 21, respectively. Blood was collected for analysis of GSK3640254 before dosing on Days 19 to 21 and up to 96 hours after dosing on Day 21. Blood samples for analysis of FSH, LH and progesterone were collected before dosing on Days 1, 10, 11, 21 and 22. Ethinyl oestradiol, levonorgestrel, GSK3640254, FSH, LH and progesterone concentrations were determined using validated bioanalytical assays. Plasma assay range was 2.00–500 pg mL^{-1} for ethinyl oestradiol, 50.0–25 000 pg mL^{-1} for levonorgestrel and 3.00–1000 ng mL^{-1} for GSK3640254. Coefficient of variation values for quality control samples ranged from 2.28 to 6.90% for ethinyl oestradiol, 2.49 to 10.9% for levonorgestrel and 3.22 to 3.72% for GSK3640254. The reference upper limits of study-specific normal were 12.1 IU L^{-1} for LH and 11.6 IU L^{-1} for FSH. The reference limit for progesterone was 6.36 nmol L^{-1}. Safety and tolerability were assessed by monitoring and recording adverse events (AEs), clinical laboratory assessments, electrocardiographic results, physical examination findings and vital signs. Liver-stopping criteria of ALT levels ≥3× ULN required discontinuation of study treatment.

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[12,13]

2.4 | Data analyses

Sample size calculations were performed using the PASS 15.0.7 (NCSS; Kaysville, UT) Equivalence Tests for the Ratio of Two Means in a 2×2 Cross-Over Design option. Input parameters included 17.2% intrasubject coefficient of variability, type I error of 0.05 and true ratio for means of 0.95. Results indicated that 19 evaluable participants were required to achieve ≥90% statistical power; therefore, approximately 25 participants were planned for enrolment. Pharmacokinetic parameters were calculated by standard noncompartmental analysis using Phoenix WinNonlin software (version 8.0; Certara, Princeton, NJ, USA). Pharmacokinetic parameter values, including geometric mean, 95% confidence interval (CI) of geometric mean, standard deviation of logged data, coefficient of variation, median, minimum and maximum, were summarized by treatment. Analyses were performed on the natural logarithms of $AUC_{0\text{-}t}$, C_{max} and C_τ using linear mixed-effect models with treatment as a fixed effect, participants as random effect and measurements within participants as repeat measures. Pharmacodynamic endpoints were compared after ethinyl oestradiol/levonorgestrel administration for 13 days (Day 10) and ethinyl oestradiol/levonorgestrel plus GSK3640254 coadministration for 11 days (Day 21) and were summarized with descriptive statistics. Safety endpoints were summarized using descriptive statistics.

Statistical analyses were performed using SAS (version 9.3 or higher; SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Study population and baseline characteristics

Of the 48 individuals who were screened, 23 were enrolled; 17 (74%) completed the study. Mean age of women enrolled was 35 years and mean body mass index was 27.4 kg m^{-2} (Table 1). All women enrolled were of childbearing age, but 22% were infertile due to tubal ligation. Two of 23 women enrolled were taking hormonal contraception immediately before the start of the study. Of these 2 women, 1 had elevated liver transaminase levels but did not meet liver-stopping criteria (ALT ≥3× ULN).

Reports of elevated liver transaminase levels in 8 participants, which is described in the Safety subsection, prompted an unplanned preliminary review of the study results. This analysis by the sponsor determined that primary and key secondary objectives had been met, and no further participants were enrolled beyond the 23 who had already received study treatment. Six participants withdrew from the study: reasons for withdrawal included AEs (elevated transaminase levels that began before exposure to GSK3640254 and met liver-stopping criteria while receiving ethinyl oestradiol/levonorgestrel plus GSK3640254 [$n = 3$]), study termination by sponsor ($n = 2$; both on Day 10) and physician decision due to inability to obtain haematological sampling ($n = 1$; on Day 20). Of the 3 participants who withdrew due to AEs, 2 met liver-stopping criteria and discontinued treatment on Day 13, and the third met liver-stopping criteria and discontinued treatment on Day 15. All 6 participants who withdrew from the study were included in the pharmacokinetic, pharmacodynamic and safety analyses for the ethinyl oestradiol/levonorgestrel treatment period and were not included in the pharmacokinetic analyses for the ethinyl oestradiol/levonorgestrel plus GSK3640254 treatment period. Except for the 2 individuals who withdrew on Day 10 due to study termination, all participants were included in the pharmacodynamic and safety analyses for the ethinyl oestradiol/levonorgestrel plus GSK3640254 treatment period.

TABLE 1 Baseline demographics

Parameter	Participants ($n = 23$)
Age, mean (SD), y	34.7 (7.8)
Sex, *n* (%)	
Female	23 (100)
Infertile (of childbearing age)	5 (22)
Childbearing potential	18 (78)
Body mass index, mean (SD), kg m^{-2}	27.4 (2.9)
Height, mean (SD), cm	162.1 (6.6)
Weight, mean (SD), kg	72.2 (10)
Ethnicity, *n* (%)	
Hispanic/Latino	6 (26)
Not Hispanic/Latino	17 (74)
Race/ethnicity, *n* (%)	
Black/African American	12 (52)
White	9 (39)
American Indian/Alaska native	1 (4)
Asian	1 (4)

SD, standard deviation.

3.2 | Pharmacokinetics

Plasma pharmacokinetic parameters for ethinyl oestradiol and levonorgestrel following ethinyl oestradiol/levonorgestrel administration and coadministration of ethinyl oestradiol/levonorgestrel plus GSK3640254 are summarized in Table 2. Geometric least squares mean ratios (90% CI) for $AUC_{0\text{-}t}$, C_{max} and C_{τ} were 0.974 (0.91–1.04), 0.970 (0.83–1.13) and 1.050 (0.98–1.13), respectively, for ethinyl oestradiol and 1.069 (0.99–1.15), 1.032 (0.94–1.14) and 1.083 (1.00–1.18), respectively, for levonorgestrel. Between-participant variability for pharmacokinetic exposure parameters was moderate, with coefficients of variability across treatments ranging from 24 to 35% for ethinyl oestradiol and from 37 to 49% for levonorgestrel. With both treatments, $AUC_{0\text{-}t}$ values for ethinyl oestradiol and levonorgestrel were similar in participants with or without ALT elevations (Figure S1A, B). Ethinyl oestradiol and levonorgestrel reached maximum plasma concentrations with a median t_{max} of 2.0 hours when given alone or with GSK3640254 and declined in a biphasic manner thereafter (Figure 1, A, B). $t_{1/2}$ was not estimated for ethinyl oestradiol and levonorgestrel after ethinyl oestradiol/levonorgestrel administration due to insufficient sample collection during the terminal phase. After ethinyl oestradiol/levonorgestrel plus GSK3640254 coadministration, the geometric mean estimate for $t_{1/2}$ was 20.2 hours for ethinyl oestradiol and 30.1 hours for levonorgestrel, although sufficient terminal phase data for levonorgestrel were only available from 4 participants (Table 2). Steady-state plasma concentrations for ethinyl oestradiol and levonorgestrel were reached by Day 10 and maintained throughout ethinyl oestradiol/levonorgestrel plus GSK3640254 coadministration (Figure S2A-B).

Geometric means of GSK3640254 steady-state plasma $AUC_{0\text{-}t}$, C_{max} and C_{τ} following ethinyl oestradiol/levonorgestrel plus GSK3640254 coadministration are shown in Table 3, with between-participant coefficients of variability ranging from 23 to 30%. The GSK3640254 $AUC_{0\text{-}t}$ values were similar in participants, irrespective of ALT elevations (Figure S1C). Maximum GSK3640254 plasma concentrations occurred at a median t_{max} of 4.5 hours after ethinyl oestradiol/levonorgestrel plus GSK3640254 coadministration and declined in a monophasic manner with a geometric mean estimate for $t_{1/2}$ of 25.7 hours (Figure 1, panel C). Steady-state plasma concentrations were reached 9 days after GSK3640254 treatment (Day 19; Figure S2C).

TABLE 2 Summary of derived plasma pharmacokinetic parameters for ethinyl oestradiol and levonorgestrel

	Ethinyl oestradiol			Levonorgestrel		
Geometric mean (% CVb) [a]	Ethinyl oestradiol/levonorgestrel ($n = 23$)	Ethinyl oestradiol/levonorgestrel + GSK3640254 ($n = 17$)	Geometric LS mean ratio (90% CI)	Ethinyl oestradiol/levonorgestrel ($n = 23$)	Ethinyl oestradiol/levonorgestrel + GSK3640254 ($n = 17$)	Geometric LS mean ratio (90% CI)
$AUC_{0\text{-}t}$, h pg mL^{-1}	748.7 (25.2)	735.8 (23.6)	0.974 (0.91–1.04)	68 682 (40.3)	75 412 (40.7)	1.069 (0.99–1.15)
95% CI	672.6–833.3	652.7–829.3	–	58 067.8–81 237.4	61 662.2–92 227.8	–
C_{max}, pg mL^{-1}	70.01 (34.9)	68.47 (33.3)	0.970 (0.83–1.13)	5806 (39.3)	5948 (36.7)	1.032 (0.94–1.14)
95% CI	60.5–81.1	58.0–80.9	–	4928.6–6838.8	4953.7–7142.2	–
C_τ, pg mL^{-1}	14.83 (32.1)	15.69 (27.8)	1.050 (0.98–1.13)	1870 (49.0)	2163 (46.6)	1.083 (1.00–1.18)
95% CI	13.0–17.0	13.6–18.1	–	1529.6–2285.0	1721.6–2716.5	–
$t_{1/2}$, h	–	20.2 (17.4)	–	–	30.1 (4.2) [b]	–
95% CI	–	18.5–22.1	–	–	28.2–32.2 [b]	–
t_{max}, median (range), h	2.0 (1.0–4.0)	2.0 (1.0–4.0)	–	2.0 (0.5–4.0)	2.0 (1.0–4.0)	–

$AUC_{0\text{-}t}$, area under the plasma concentration–time curve from time zero to the end of the dosing interval at steady state; CI, confidence interval; C_{max}, maximum observed concentration; C_τ, plasma concentration at the end of the dosing interval; %CVb, between-participant coefficient of variation; LS, least squares; $t_{1/2}$, apparent terminal phase half-life; t_{max}, time to C_{max}.

[a]Except where noted for t_{max}.

[b]$n = 4$ with sufficient terminal phase data for estimation of $t_{1/2}$.

FIGURE 1 Mean linear plasma concentration–time profiles by treatment for (A) ethinyl oestradiol, (B) levonorgestrel and (C) GSK3640254. The numbers of participants with evaluable values were 23 for ethinyl oestradiol/levonorgestrel and 17 for ethinyl oestradiol/levonorgestrel + GSK3640254. Error bars indicate standard deviation

TABLE 3 Summary of derived plasma pharmacokinetic parameters for GSK3640254

Geometric mean (%CVb) [a]	Ethinyl oestradiol/levonorgestrel + GSK3640254 ($n = 17$)
$AUC_{0\text{-}t}$, h μg mL^{-1}	30.22 (23.1)
95% CI	26.9–34.0
C_{max}, μg mL^{-1}	1.78 (30.4)
95% CI	1.5–2.1
C_τ, μg mL^{-1}	0.97 (27.1)
95% CI	0.8–1.1
$t_{1/2}$, h	25.7 (19.1) [b]
95% CI	23.0–28.6 [b]
t_{max}, median (range), h	4.5 (3.5–24.0)

$AUC_{0\text{-}t}$, area under the plasma concentration–time curve from time zero to the end of the dosing interval at steady state; CI, confidence interval; C_{max}, maximum observed concentration; C_τ, plasma concentration at the end of the dosing interval; %CVb, between-participant coefficient of variation; $t_{1/2}$, apparent terminal phase half-life; t_{max}, time to C_{max}.

[a]Except where noted for t_{max}.

[b]$n = 14$ with sufficient terminal phase data for estimation of $t_{1/2}$.

3.3 | Pharmacodynamics

Three participants had on-treatment progesterone levels > ULN for the follicular phase (progesterone ULN, 6.36 nmol L^{-1}). In 2 of these participants, increased progesterone levels occurred on Day 10 after treatment with ethinyl oestradiol/levonorgestrel alone, with progesterone levels ranging from 6.68 to 9.19 nmol L^{-1}. The third participant had an increase in progesterone level to 7.98 nmol L^{-1} on Day 22 after ethinyl oestradiol/levonorgestrel plus GSK3640254 coadministration. However, all participants had on-treatment FSH and LH values < ULN for the follicular phase.

3.4 | Safety

No deaths or serious AEs were reported. Fourteen participants reported AEs during the study, occurring after ethinyl oestradiol/levonorgestrel administration alone in 5 participants and after ethinyl oestradiol/levonorgestrel plus GSK3640254 coadministration in 12 participants (Table 4). No AEs were reported during the run-in period. The most commonly reported AEs were elevated liver transaminase levels (22%), headache (17%) and metrorrhagia (13%). All AEs were grade 1 in intensity, except in 5 participants (22%) who reported grade 2 elevated transaminase levels. Nine participants (39%) reported 18 AEs considered to be drug related, occurring after ethinyl oestradiol/levonorgestrel administration alone in 5 participants (8 events) and after ethinyl oestradiol/levonorgestrel plus GSK3640254 coadministration in 6 participants (10 events). The most commonly reported drug-related AEs were increased asymptomatic liver transaminase levels ($n = 4$ after ethinyl oestradiol/levonorgestrel alone and $n = 1$ after ethinyl oestradiol/levonorgestrel + GSK3640254), metrorrhagia ($n = 2$ after ethinyl oestradiol/levonorgestrel alone and $n = 1$ after ethinyl oestradiol/levonorgestrel + GSK3640254) and infrequent bowel movements ($n = 2$ after ethinyl oestradiol/levonorgestrel + GSK3640254).

Eight participants, including the 5 participants with increased liver transaminase levels already described, developed asymptomatic ALT levels > ULN (ALT ULN, 45 IU L^{-1}; Figure S3A). The highest 3 ALT

TABLE 4 Summary of adverse events (AEs)

Preferred term, *n* (%)	Ethinyl oestradiol/levonorgestrel (*n* = 23)	Ethinyl oestradiol/levonorgestrel + GSK3640254 (*n* = 21)	Total (*n* = 23)
Total AEs [a]			
Any event	5 (22)	12 (57)	14 (61) [b]
Elevated transaminase levels	4 (17)	1 (5)	5 (22)
Headache	0	4 (19)	4 (17)
Metrorrhagia	2 (9)	1 (5)	3 (13)
Abdominal pain	1 (4)	1 (5)	2 (9)
Diarrhoeal	0	2 (10)	2 (9)
Infrequent bowel movements	0	2 (10)	2 (9)
Pruritus	0	2 (10)	2 (9)
Drug-related AEs			
Elevated transaminase levels	4 (17) [c]	1 (5) [d]	5 (22)
Metrorrhagia	2 (9)	1 (5)	3 (13)
Infrequent bowel movements	0	2 (10)	2 (9)
Abdominal pain	1 (4)	0	1 (4)
Diarrhoea	0	1 (5)	1 (4)
Drug eruption	0	1 (5)	1 (4)
Dry skin	0	1 (5)	1 (4)
Frequent bowel movements	0	1 (5)	1 (4)
Headache	0	1 (5)	1 (4)
Menorrhagia	1 (4)	0	1 (4)
Pruritus	0	1 (5)	1 (4)

[a]Each AE reported in >1 participant.
[b]Indicates number of participants who reported any AE during the study.
[c]Three participants met liver-stopping criteria and were withdrawn from the study.
[d]Participant met liver-stopping criteria after receiving all study treatments and did not withdraw from the study.

elevations in any of these 8 participants at any time point ranged from 139 to 207 IU L^{-1}. Among the 8 participants with ALT elevations, 4 began to display an increase in ALT levels with ethinyl oestradiol/levonorgestrel alone, 3 of whom met liver-stopping criteria (ALT ≥3× ULN). The other 4 participants had increases in ALT levels after 10 days of treatment with ethinyl oestradiol/levonorgestrel plus GSK3640254. The highest 3 elevations of aspartate aminotransferase (AST) levels in any participant at any time point ranged from 62 to 89 IU L^{-1} (Figure S3B). Each of the 8 participants had liver enzyme levels return to within normal ranges and remained asymptomatic without any long-term clinical sequalae.

Special-interest AEs associated with gastrointestinal and psychiatric disorders were reported by 5 participants (22%). The AEs of special interest considered to be drug related included abdominal pain, diarrhoea, and frequent or infrequent bowel movements. Except for elevated liver transaminase levels, including ALT and AST values, no clinically relevant mean changes from baseline in laboratory values, electrocardiographic findings or vital signs were observed.

4 | DISCUSSION

As with other antiretrovirals for treatment of HIV-1 infection, the next-generation maturation inhibitor GSK3640254 is expected to be coadministered with many common medications, including combined oral contraceptives, in women living with HIV-1 infection. In this phase I study, we demonstrated that GSK3640254 did not affect pharmacokinetics (concentrations of ethinyl oestradiol and levonorgestrel) or pharmacodynamic interactions (concentrations of FSH, LH and progesterone) of ethinyl oestradiol and levonorgestrel when coadministered with a combined oral contraceptive containing ethinyl oestradiol/levonorgestrel as described in further detail below.

Mean steady-state pharmacokinetics of ethinyl oestradiol and levonorgestrel were not affected by coadministration of ethinyl oestradiol/levonorgestrel plus GSK3640254 in the presence of a moderate-fat meal, because the geometric least squares mean ratio 90% CIs for $AUC_{0\text{-}t}$, C_{max} and C_{τ} were within the no-effect bounds of 0.80 to 1.25 for both ethinyl oestradiol and levonorgestrel.[14] Median t_{max} for ethinyl oestradiol and levonorgestrel was also unchanged with ethinyl oestradiol/levonorgestrel plus GSK3640254 treatment. Following coadministration of ethinyl oestradiol/levonorgestrel plus GSK3640254, steady-state GSK3640254 plasma exposure values for $AUC_{0\text{-}t}$ (30.22 h μg mL^{-1}), C_{max} (1.78 μg mL^{-1}) and C_{τ} (0.97 μg mL^{-1}) were similar to those previously observed for repeat doses of GSK3640254 200 mg alone for 14 days in healthy male participants (ClinicalTrials.gov identifier: NCT03231943).[9] Based on lack of drug interactions observed in the study, GSK3640254 and oral contraceptives containing ethinyl oestradiol/levonorgestrel could be coadministered without dose modifications. These results support the inclusion of women taking oral contraceptives in future GSK3640254 clinical studies, which is important given that women are often underrepresented in HIV-1 ART clinical trials.[15]

The impact of GSK3640254 on the pharmacodynamics of ethinyl oestradiol/levonorgestrel was measured by suppression of ovulation as indicated by FSH, LH and progesterone levels. The isolated elevations of progesterone levels in 3 participants were likely due to assay variability and probably not biologically or clinically indicative of ovulation because on-treatment FSH and LH values were < ULN for the follicular phase in all participants. No apparent effect of GSK3640254 was observed on the pharmacodynamics of ethinyl oestradiol/levonorgestrel.

Coadministration of ethinyl oestradiol/levonorgestrel plus GSK3640254 did not demonstrate any major tolerability findings when given to healthy participants. Asymptomatic elevations in ALT and AST levels were observed during coadministration of GSK3640254 plus a combination oral contraceptive containing ethinyl oestradiol and levonorgestrel. Pharmacokinetic parameters for GSK3640254, ethinyl oestradiol, or levonorgestrel did not demonstrate an interaction between GSK3640254 and ethinyl oestradiol/levonorgestrel, including in participants with or without increased ALT levels. Oestrogen-containing oral contraceptives are associated with cholestatic liver injury.[16] Historically, mild-to-moderate, transient, asymptomatic increases in transaminases have been observed with oral contraceptives and more frequently occur during the early months of oral contraceptives initiation.[17] A temporal association was observed between liver enzyme increases and new administration of ethinyl oestradiol/levonorgestrel to the participants before the short run-in period (Figure S3). Indeed, none of the participants with an AE of increased transaminase level reported taking hormonal contraception ≤28 days before study entry; therefore, the oral contraceptives initiated during the study may have resulted in an increased probability of drug-related liver enzyme elevations. In addition, although elevated liver enzymes are discussed in the context of concomitant hepatitis C treatment in the US package insert for the oral contraceptive used in the study,[18] liver function disturbance is listed in the UK summary of product characteristics for the equivalent combined oral contraceptive.[19] Ethinyl oestradiol-containing oral contraceptives were also associated with elevated liver transaminases in a 2018 study.[20] Further, an AE of increased transaminases was reported in only 1 of 63 healthy participants who received GSK3640254 200 mg across 3 other phase I studies.[9,21,22]

There are some limitations to this study. Exposing women to hormonal contraception for a longer period of time, either as an explicit inclusion criterion or a longer run-in period, may result in liver transaminase changes occurring, being detected and probably resolving. Two women were taking hormonal contraception immediately before the start of the study, and there was not a washout period before receiving ethinyl oestradiol/levonorgestrel in the run-in period. Before receiving all planned doses of ethinyl oestradiol/levonorgestrel plus GSK3640254, 6 participants withdrew from the study. Due to reduced study enrolment and withdrawals, 17 participants completed the study, fewer than the 19 evaluable participants required to achieve ≥90% statistical power according to the sample size calculations. However, reduction in power for testing the equivalence of these ratios was minimal (from 90.7% power with 19 participants to

87.2% power with 17 participants when holding constant all other input parameters previously described in the Data Analyses section). Thus, the study remained adequately powered, and study conclusions regarding lack of effect of GSK3640254 administration on the steady-state pharmacokinetics of ethinyl oestradiol and levonorgestrel in healthy women were unchanged. As this study evaluated the interaction between GSK3640254 and a specific combined oral contraceptive containing ethinyl oestradiol and levonorgestrel, it is unclear whether these results can be extended to combined oral contraceptives with different formulations. Most oestrogens and progestins are metabolized by cytochrome P450 enzymes, which GSK3640254 minimally inhibited or induced in in vitro studies.[23] Together with the lack of interaction observed between GSK3640254 and the oestrogen and progestin evaluated in the present study, it is unlikely that drug interactions between GSK3640254 and other formulations of combined oral contraceptives will occur.

GSK3640254 did not affect steady-state pharmacokinetics or pharmacodynamics of ethinyl oestradiol and levonorgestrel when coadministered with ethinyl oestradiol/levonorgestrel, a combined oral contraceptive agent, in healthy women. No major tolerability findings definitively linked to GSK3640254 were observed, and elevated liver transaminase level AEs reported during ethinyl oestradiol/levonorgestrel with or without GSK3640254 coadministration were probably due to ethinyl oestradiol/levonorgestrel administration. Coadministration of GSK3640254 with ethinyl oestradiol/levonorgestrel did not result in breakthrough ovulation as measured by FSH, LH and progesterone levels. Therefore, coadministration of GSK3640254 and combined oral contraceptives containing ethinyl oestradiol/levonorgestrel appears to be well tolerated and suitable for combination use in HIV therapy.

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COMPETING INTERESTS

T.P. and J.X. were employees of GlaxoSmithKline at the time of the study and may hold stock in the company. T.J.G., F.H. and L.B. are employees of and own stock in GlaxoSmithKline. S.R.J. is an employee of ViiV Healthcare. M.J., M.L. and S.M. are employees of ViiV Healthcare and own stock in GlaxoSmithKline. E.Z. and L.W. are employees of PPD. T.T.P. was an employee of PPD at the time of the study.

CONTRIBUTORS

All authors have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; been involved in drafting the manuscript or revising it critically for important intellectual content; given final approval of the version to be published; participated sufficiently in the work to take public responsibility for appropriate portions of the content; and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICS APPROVAL

The study was designed and conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice following the principles of the Declaration of Helsinki. IntegReview IRB (Austin, TX, USA) approved the study protocol and conduct.

PATIENT CONSENT

All participants provided written informed consent and could withdraw from the study at any time.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov, NCT03984825.

SOCIAL MEDIA TEXT

GSK3640254 plus combined oral contraceptives was not associated with drug–drug interactions or major tolerability findings.

DATA AVAILABILITY STATEMENT

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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