Received: 8 October 2020 | Revised: 18 December 2020 | Accepted: 28 December 2020

DOI: 10.1111/bcp.14759

ORIGINAL ARTICLE

Phase I evaluation of pharmacokinetics and tolerability of the HIV-1 maturation inhibitor GSK3640254 and dolutegravir in healthy adults

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Funding information
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Aims: GSK3640254, a novel, next-generation maturation inhibitor effective against a range of HIV polymorphisms with no cross-resistance to current antiretroviral therapy, could potentially be coadministered with dolutegravir as a 2-drug regimen. In this phase I study, pharmacokinetics and tolerability of GSK3640254 plus dolutegravir were assessed.

Methods: Healthy participants received dolutegravir 50 mg once daily (QD) on Days 1–5 in period 1, GSK3640254 200 mg QD on Days 1–7 in period 2, and dolutegravir 50 mg plus GSK3640254 200 mg QD on Days 1–7 in period 3. All treatments were administered with a moderate-fat meal 30 minutes prior to dosing. Pharmacokinetics parameters were derived by noncompartmental methods, and geometric mean ratios (GMRs) and 90% confidence intervals (CIs) were derived using linear mixed effects models. Adverse events, laboratory measurements, electrocardiography and vital signs were monitored.

Results: Sixteen participants completed the study. GMRs (90% CIs) for dolutegravir area under the plasma concentration–time curve from time 0 to the end of the dosing interval at steady state, maximum observed concentration and plasma concentration at the end of the dosing interval were 1.17 (1.118–1.233), 1.09 (1.044–1.138) and 1.24 (1.160–1.315), respectively. The GMRs (90% CIs) for GSK3640254 were 1.04 (0.992–1.094), 0.99 (0.923–1.065) and 0.10 (0.939–1.056), respectively. Dolutegravir plus GSK3640254 coadministration did not meaningfully alter steady-state exposure to dolutegravir or GSK3640254. No clinically significant trends in tolerability or safety were observed.

Conclusion: Coadministration of GSK3640254 with dolutegravir did not result in clinically significant drug interaction and was well tolerated.

Data in this manuscript were presented in part at the International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs 2020; September 28-30, 2020; Virtual.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT03816696.

Principal investigator: The authors confirm that the PI for this paper is Theresa T. Pham and that she had direct clinical responsibility for patients.

KEYWORDS
clinical pharmacology, drug interactions, drug safety, HIV/AIDS

1 | INTRODUCTION

Current treatment regimens for HIV include use of antiretroviral therapy, most of which targets reverse transcriptase, protease or integrase proteins.[1] However, despite increased availability and recent advancements in antiretroviral therapy, drug resistance and intolerability may occur and can result in treatment failure.[2] In addition, HIV regimens may be complex and involve a combination of several agents.[3] Addition of a new class of therapeutic agents for people living with HIV infection would be a beneficial addition to the HIV treatment armamentarium.

Maturation is the last step in the lifecycle of HIV-1.[4] This process allows for newly released HIV particles to become infectious due to the proteolytic cleavage of HIV-1 structural protein (Gag) precursors via viral protease. As such, viral maturation is a crucial target for therapeutic intervention because disruption of HIV-1 maturation results in noninfectious viral particles. New therapeutic agents, termed maturation inhibitors, limit HIV-1 maturation by inhibiting protease-mediated cleavage of capsid-spacer peptide 1 in the Gag polyprotein.[4] In vitro analyses and phase IIa/IIb trials have shown that pharmacologic inhibition of maturation impedes replication of HIV-1 isolates, resulting in a beneficial antiviral response.[2–6] However, because HIV therapies, including maturation inhibitors, would be administered in combination with other drug classes, it is crucial to understand the effects of potential interactions or changes in exposure.

GSK3640254 is a novel, next-generation maturation inhibitor that has demonstrated inhibition across HIV-1 subtypes with no cross-resistance to currently approved antiretroviral treatments.[7] In healthy participants administered GSK3640254, the most commonly reported adverse event was headaches[7]; additional data regarding adverse events in people living with HIV receiving GSK3640254 are forthcoming. A 2-drug combination of GSK3640254 and **dolutegravir**, which is an integrase inhibitor with a high barrier to resistance, may be a beneficial and simplified treatment regimen for patients living with HIV infection.[8] Notably, GSK3640254 is an inhibitor of **uridine diphosphate glucuronosyltransferase (UGT) 1A1** in vitro (half maximal inhibitory concentration of 3.9 μM); clinical drug–drug interactions via this inhibitory mechanism are possible. Dolutegravir is primarily metabolized by UGT1A1, so it is unclear whether coadministration of dolutegravir and GSK3640254 is associated with increased dolutegravir plasma concentrations due to enzymatic inhibition. Here, we report the pharmacokinetic (PK) and tolerability data from a phase I, 2-way drug interaction study of GSK3640254 and dolutegravir in healthy individuals.

What is already known about this subject

- Maturation inhibitors disrupt the lifecycle of HIV-1 by inhibiting viral maturation and are novel targets for therapeutic regimens.
- GSK3640254 is a novel, next-generation maturation inhibitor capable of inhibition across a broad range of HIV-1 GAG polymorphisms.

What this study adds

- GSK3640254, alone or in combination with the integrase inhibitor dolutegravir, was not associated with drug–drug interactions requiring contraindication, dose modification, or major safety/tolerability findings.
- Combination therapy with these agents may be suitable for individuals living with HIV infection.

2 | METHODS

2.1 | Study design

This was a phase I, open-label, fixed-sequence, 2-way drug interaction study to investigate the PK interactions and tolerability and safety of GSK3640254 and dolutegravir administered alone and in combination in healthy adults (NCT03816696). Participants were screened within 28 days before the first dose of study treatment. Participants first received dolutegravir 50 mg once daily (QD) for 5 days (period 1). Following a washout period of 4 days, participants then received GSK3640254 200 mg QD for 7 days (period 2). Next, participants received combined treatment of dolutegravir 50 mg and GSK3640254 200 mg QD for 7 days (period 3). The maximum projected clinical dose of GSK3640254 is 200 mg QD, and dolutegravir 50 mg QD is the approved dose for people living with HIV infection.[9] All participants fasted overnight for ≥8 hours prior to dosing and received a moderate-fat meal 30 minutes prior to dosing, which occurred ≤5 minutes from meal consumption.

This study was designed in accordance with the US Food and Drug Administration Guidance for Industry, Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications. Key inhibitors are hyperlinked to their entries in the IUPHAR/BPS **Guide to Pharmacology**.[10] These descriptions are also listed in the *Concise Guide to Pharmacology 2017/18*.[11]

2.2 | Study participants

Eligibility was determined by medical history, physical examination, laboratory values and cardiac monitoring. Eligible participants were healthy men and women aged 18–55 years (inclusive) with a body weight of ≥50 kg (men) or ≥45 kg (women) and a body mass index of 18.5–31.0 kg/m^2 (inclusive). Women who were not of childbearing potential (e.g. postmenopausal, documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy), pregnant or breastfeeding were eligible for the study.

Exclusion criteria were related to medical history (e.g. history of cardiac, liver, gastrointestinal, psychiatric disorders) and laboratory values, including a positive finding on HIV, hepatitis B or hepatitis C testing. Individuals were excluded if they received concomitant treatments that could affect the PK of the investigational drug. Other exclusion criteria included regular alcohol or tobacco use and sensitivity to study treatments.

2.3 | Ethics approval

This study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice and US 21 Code of Federal Regulations 312.3(b). Study protocol and conduct were approved by IntegReview IRB (Austin, TX, USA).

2.4 | Patient consent

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

2.5 | Study assessments

The primary endpoints were to assess the effect of dolutegravir on the steady-state PK of GSK3640254 and vice versa. Secondary endpoints included assessment of safety and tolerability of dolutegravir and GSK3640254, alone or in combination, as well as to characterize the steady-state PK of GSK3640254 and dolutegravir alone or in combination. Safety and tolerability were assessed by monitoring adverse events (AEs), clinical laboratory values, vital sign measurements, electrocardiographic results and physical examination findings.

For analysis of dolutegravir, PK blood samples were collected before dosing (0 hour) on Days 2 to 5 in period 1 and Days 2 to 7 in period 3. Postdose samples were collected ≤72 hours after dolutegravir dosing on Day 5 in period 1 and after dolutegravir dosing on Day 7 in period 3 (1, 1.5, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48 and 72 h for both periods).

For analysis of GSK3640254, PK blood samples were collected before dosing (0 hour) on Days 4 to 7 in periods 2 and 3. Postdose samples were collected ≤24 hours after GSK3640254 dosing on Day 7 in period 2 and ≤96 hours after GSK3640254 dosing on Day 7 in period 3 (1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12 and 24 h for both periods, with additional samples at 48, 72 and 96 h for period 3).

2.6 | Data analyses

Sample size calculations were based on a 30% intrasubject coefficient of variation for dolutegravir and 38% for GSK3640254, and sensitivity analyses were run to estimate precision and confidence intervals (CIs). Analyses were performed on natural logarithms of the primary plasma PK endpoints (area under the plasma concentration–time curve from time 0 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_t]) using linear mixed-effect models with period as a fixed effect, participant as a random effect and measurements within participant as repeated measures. Secondary plasma PK parameters (time to first C_{max} [T_{max}] and terminal elimination half-life [$t_{1/2}$]) were estimated for dolutegravir (periods 1 and 3) and GSK3640254 (periods 2 and 3), and they were summarized using descriptive statistics. Safety endpoints were summarized using descriptive statistics.

2.7 | Data sharing

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

TABLE 1 Baseline demographics

Parameter	Participants (n = 16)
Age, mean (SD), y[a]	36.7 (10.7)
Sex, *n* (%)	
Female	1 (6)
Male	15 (94)
Body mass index (SD), kg/m^2	26.8 (2.8)
Height (SD), cm	170.3 (5.6)
Weight (SD), kg	77.9 (9.9)
Ethnicity, *n* (%)	
Hispanic/Latino	9 (56)
Not Hispanic/Latino	7 (44)
Race/Ethnicity, *n* (%)	
Asian heritage	2 (13)
Black/African American	3 (19)
White/Caucasian/European heritage	11 (69)

SD, standard deviation.

[a]Age was imputed if full date of birth was not provided.

3 | RESULTS

3.1 | Study population

A total of 30 patients were screened, of whom 16 enrolled and completed the study. A summary of participant baseline demographics is summarized in Table 1. Most participants were men (94%) and white (69%). Mean age was 37 years, and mean body mass index was 27 kg/m^2.

3.2 | Pharmacokinetics

Mean steady-state dolutegravir plasma exposure values for $AUC_{0\text{-}t}$ and C_{max} were similar when dolutegravir was administered alone or in combination with GSK3640254 200 mg in the presence of a moderate-fat meal (Table 2). Mean C_t values for dolutegravir plus GSK3640254 were slightly increased *vs.* dolutegravir alone, although this difference was not clinically meaningful. The $t_{1/2}$ was comparable for dolutegravir alone and dolutegravir plus GSK3640254 (14.5 and 14.7 h, respectively), and between-participant variability (%CVb) for exposure parameters ($AUC_{0\text{-}t}$, C_{max} and C_t) was low to moderate, ranging from 16.5 to 31.1% across treatments. When GSK3640254 was coadministered with dolutegravir, steady-state dolutegravir plasma exposures were not meaningfully different *vs.* dolutegravir alone. Geometric mean ratios for dolutegravir $AUC_{0\text{-}t}$, C_{max} and C_t are shown in Table 2.

Similarly, mean steady-state GSK3640254 plasma exposure values for $AUC_{0\text{-}t}$, C_{max} and C_t were comparable when GSK3640254 was administered alone or in combination with dolutegravir 50 mg in the presence of a moderate-fat meal (Table 3). The %CVb for $AUC_{0\text{-}t}$, C_{max} and C_t were also low to moderate, ranging from 26.4 to 38.3% across treatments. The $t_{1/2}$ was not determined for GSK3640254 alone but was 23.4 hours for dolutegravir plus GSK3640254. Dolutegravir did not affect the steady-state GSK3640254 exposure. Geometric mean ratios for GSK3640254 $AUC_{0\text{-}t}$, C_{max} and C_t are shown in Table 3.

Maximum concentration of dolutegravir when administered alone or in combination with GSK3640254 occurred at a median of 3 hours after administration and declined in a monophasic manner thereafter

TABLE 2 Summary of derived plasma pharmacokinetic parameters for dolutegravir

Geometric mean (SD Ln)[a]	Dolutegravir 50 mg (*n* = 16)	Dolutegravir 50 mg + GSK3640254 200 mg (*n* = 16)
$AUC_{0\text{-}t}$, h•μg/mL	64.63 (1.22)	75.86 (1.25)
95% CI	58.12–71.86	67.31–85.50
%CVb	20.1	22.7
Ratio (90% CI)[b]	—	1.17 (1.12–1.23)
C_{max}, μg/mL	4.96 (1.18)	5.41 (1.19)
95% CI	4.55–5.42	4.94–5.92
%CVb	16.5	17.2
Ratio (90% CI)[b]	—	1.09 (1.04–1.14)
C_t, μg/mL	1.37 (1.35)	1.70 (1.36)
95% CI	1.17–1.61	1.44–1.99
%CVb	30.6	31.1
Ratio (90% CI)[b]	—	1.24 (1.16–1.32)
$t_{1/2}$, h	14.49 (1.13)	14.69 (1.13)
95% CI	13.61–15.43	13.77–15.67
%CVb	11.8	12.1
T_{max} (median [min, max]), h	3.0 (1.0, 4.5)	3.0 (1.0, 4.5)

$AUC_{0\text{-}t}$, area under the plasma concentration–time curve from time 0 to the end of the dosing interval at steady state; CI, confidence interval; C_{max}, maximum observed concentration; C_t, plasma concentration at the end of the dosing interval; %CVb, between-participant variability; SD Ln, standard deviation of natural logarithm transformed data; $t_{1/2}$, terminal elimination half-life; T_{max}, time to first occurrence of maximum observed concentration.

[a]Except where noted.

[b]Ratio calculation: dolutegravir 50 mg + GSK3640254 200 mg/dolutegravir 50 mg.

TABLE 3 Summary of derived plasma pharmacokinetic parameters for GSK3640254

Geometric mean (SD Ln)[a]	GSK3640254 200 mg (*n* = 16)	Dolutegravir 50 mg + GSK3640254 200 mg (*n* = 16)
$AUC_{0\text{-}t}$, h•μg/mL	26.72 (1.37)	27.84 (1.34)
95% CI	22.6–31.6	23.8–32.6
%CVb	32.3	30.1
Ratio (90% CI)[b]	—	1.04 (0.99–1.09)
C_{max}, μg/mL	1.68 (1.30)	1.66 (1.30)
95% CI	1.5–1.9	1.4–1.9
%CVb	26.4	26.8
Ratio (90% CI)[b]	—	0.99 (0.92–1.07)
C_t, μg/mL	0.86 (1.45)	0.86 (1.40)
95% CI	0.7–1.1	0.7–1.0
%CVb	38.3	34.1
Ratio (90% CI)[b]	—	1.00 (0.94–1.06)
$t_{1/2}$, h	ND	23.42 (1.16)
95% CI	ND	21.6–25.4
%CVb	ND	15.0
T_{max} (median [min, max]), h	5.0 (3.5, 8.0)	5.0 (3.5, 8.0)

$AUC_{0\text{-}t}$, area under the plasma concentration–time curve from time 0 to the end of the dosing interval at steady state; CI, confidence interval; C_{max}, maximum observed concentration; C_t, plasma concentration at the end of the dosing interval; %CVb, between-participant variability; ND, not determined; SD Ln, standard deviation of natural logarithm transformed data; $t_{1/2}$, terminal elimination half-life; T_{max}, time to first occurrence of maximum observed concentration.

[a]Except where noted.

[b]Ratio calculation: dolutegravir 50 mg + GSK3640254 200 mg/GSK3640254 200 mg.

(Figure 1). Similarly, maximum concentrations for GSK3640254 alone or in combination with dolutegravir occurred at a median of 5 hours after administration and declined in a similar manner (Figure 2). Steady state was reached by Day 4 for all treatment phases, confirming the appropriateness of the study design and washout period.

3.3 | Safety

No deaths, serious AEs, or AEs leading to withdrawal were reported. All AEs were considered mild in intensity, and none were considered related to study treatment. Five participants (31%) reported 10 AEs during the study (Supplementary Table). One participant (6%) reported 1 AE after receiving dolutegravir, 3 participants (19%) reported 4 AEs after receiving GSK3640254 and 2 participants (13%) reported 5 AEs after receiving dolutegravir plus GSK3640254. Most AEs were reported by 1 participant each. Contact dermatitis at the electrocardiographic electrode site was reported by 2 participants: 1 event occurred after GSK3640254 alone and 1 event after dolutegravir plus GSK3640254. These same 2 participants also reported other forms of dermatitis (one reported contact dermatitis behind both ears and 1 reported dermatitis of the right forearm) after dolutegravir plus GSK3640254. The majority of AEs was considered resolved; however, 1 participant reported intermittent, mild anxiety-related symptoms unrelated to study treatment and was referred to a physician for ongoing care. No clinically relevant mean changes from baseline were observed in chemistry, haematology or urinalysis values during the study, and no apparent treatment-related trends were observed. No findings of concern were identified for electrocardiographic parameters.

4 | DISCUSSION

Maturation is the final stage in the lifecycle of HIV-1 and is an attractive target for novel therapeutic regimens.[4] In this phase I trial, PK, safety and tolerability of dolutegravir and GSK3640254, alone and in combination, were evaluated in healthy participants. Although a clinically meaningful interaction between dolutegravir and GSK3640254 was not expected, evaluation of any potential drug interaction was still crucial, because these agents could be used in combination for treatment of HIV infection, in particular as part of a fixed-dose, 2-drug regimen. No meaningful alterations were observed to the PK or safety profile of either drug alone or in combination.

GSK3640254 did not meaningfully affect steady-state PK of dolutegravir, and $AUC_{0\text{-}t}$ and C_{max} mean values were similar for dolutegravir alone or in combination with GSK3640254. The 90% CIs for the ratios for $AUC_{0\text{-}t}$, C_{max} and C_t were also within the no-effect

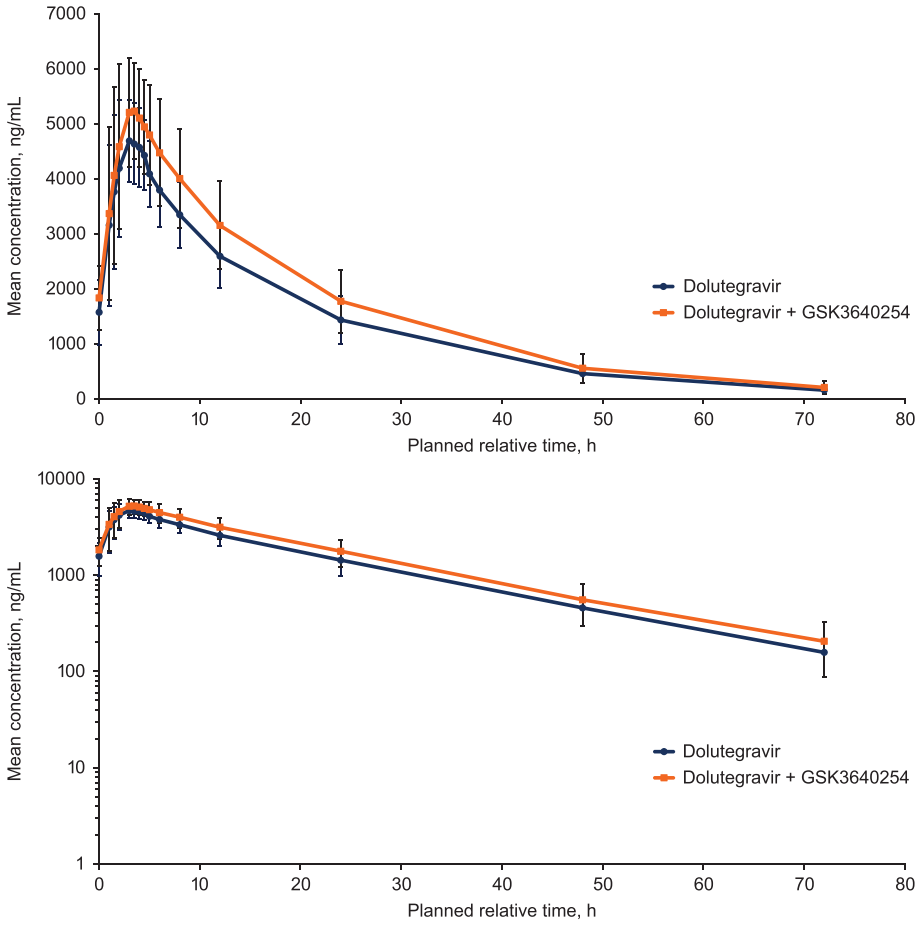

FIGURE 1 Mean linear and semi-log plasma concentration time plots for dolutegravir by treatment. Error bars indicate standard deviation

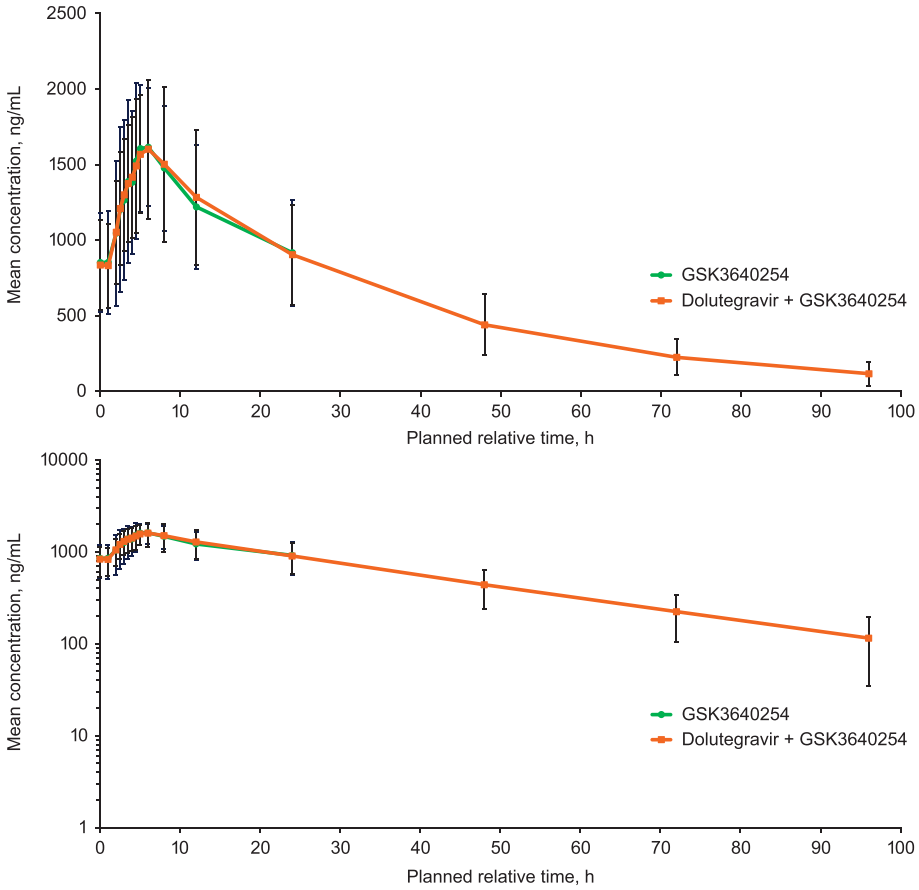

FIGURE 2 Mean linear and semi-log plasma concentration time plots for GSK3640254 by treatment. Error bars indicate standard deviation

bounds of 0.80–1.25.[12] The slightly increased dolutegravir C_t values for dolutegravir plus GSK3640254 could be attributed to mild inhibition of UGT1A1-mediated clearance of dolutegravir, but this increase was not clinically meaningful and suggests that no dosing adjustments are needed. Furthermore, $t_{1/2}$ values for dolutegravir were comparable across treatments.

Similarly, steady-state PK of GSK3640254 was not meaningfully affected by coadministration with dolutegravir in healthy participants. Mean steady-state plasma exposure values for $AUC_{0\text{-}t}$, C_{max} and C_t were similar when GSK3640254 was administered alone or in combination with dolutegravir. The lower bound of the 90% CIs for $AUC_{0\text{-}t}$ and C_{max} were also within the 0.80–1.25 bounds of no effect.[12] Although $t_{1/2}$ was not determined for GSK3640254 alone, the geometric mean $t_{1/2}$ for GSK3640254 plus dolutegravir was 23.4 hours. This value is similar to a $t_{1/2}$ value for GSK3640254 administered alone that was reported in a previous study on Day 14 of treatment (22.1 h).[7]

GSK3640254 alone or in combination with dolutegravir did not demonstrate any major tolerability or safety findings. No clinically significant trends in safety or tolerability were observed, including AEs, laboratory abnormalities, vital signs or findings on electrocardiography.

There are some limitations to this study. Although observed PK variability was within projections, sample sizes were small and most participants were men (n = 15 [94%]) and white (n = 11 [69%]), potentially limiting the generalizability of these findings. Women of childbearing potential were ineligible to participate due to the unknown effect of GSK3640254 on fetal development at the time of this study.

Both dolutegravir and GSK3640254, administered alone or in combination, were not associated with drug–drug interactions or major tolerability or safety findings. The results of this study suggest that dolutegravir and GSK3640254 may be suitable for combined use in patients living with HIV infection and in future clinical trials of HIV treatment.

ACKNOWLEDGEMENTS

This study was funded by ViiV Healthcare. Editorial assistance was provided under the direction of the authors by Deirdre Rodeberg, PhD, and Sherri Damlo, ELS, MedThink SciCom, and was funded by ViiV Healthcare. This study was funded by ViiV Healthcare.

COMPETING INTERESTS

T.P.D., J.X., T.J.G. and L.B. are employees of and own stock in GlaxoSmithKline. S.R.J., M.J., M.L. and S.M. are employees of ViiV Healthcare. M.J., M.L. and S.M. own stock in GlaxoSmithKline. E.Z, L. W. and T.T.P. are employees of PPD.

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.

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 online in the Supporting Information section at the end of this article.

How to cite this article: Pene Dumitrescu T, Joshi SR, Xu J, et al. Phase I evaluation of pharmacokinetics and tolerability of the HIV-1 maturation inhibitor GSK3640254 and dolutegravir in healthy adults. *Brit Jnl Clinical Pharma*. 2021;87(9):3501–3507. https://doi.org/10.1111/bcp.14759