ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology®

Relative Bioavailability and Food Effect of GSK3640254 Tablet and Capsule Formulations in Healthy Participants

Clinical Pharmacology in Drug Development
2022, 11(5) 632–639

DOI: 10.1002/cpdd.1051

Mark Johnson[1], Teodora Pene Dumitrescu[2,†], Samit R. Joshi[3], Ashwin Mathew[2], Veronica Bainbridge[4], Joyce Zhan[2], and Max Lataillade[3]

Abstract

GSK3640254 is a next-generation maturation inhibitor with demonstrated potency across HIV-1 subtypes and a high barrier to emergent resistance. This phase I, 2-part, randomized, open-label study (ClinicalTrials.gov identifier, NCT04263142) in healthy participants assessed the relative bioavailability of a single dose of GSK3640254 200 mg in tablet and capsule formulations (part 1) and the effect of food on the pharmacokinetic profile of the tablet formulation (part 2). Overall, 39 participants were randomized to treatment (part 1, n = 18; part 2, n = 21). All participants in part 1 completed the study; 2 participants in part 2 withdrew before study completion (adverse event, n = 1; physician decision, n = 1). In part 1, plasma exposures of the GSK3640254 tablet formulation were not meaningfully different from those of the capsule formulation when administered in the presence of a moderate-fat meal. In part 2, GSK3640254 plasma exposures increased by ≈3- to 4-fold under high- and moderate-fat conditions, respectively, compared with fasted conditions. No major safety or tolerability findings were observed. The highest incidence of adverse events (24%) was reported under high-fat conditions. Taken together, these data support the use of the tablet formulation coadministered with food in the clinical development of GSK3640254 for treatment of HIV-1.

Keywords

food effect, GSK3640254, maturation inhibitor, pharmacokinetics, relative bioavailability

Although current antiretroviral therapies have been successful in markedly reducing morbidity and prolonging survival among individuals with HIV, challenges with emergent resistance, drug-drug interactions, and intolerability have resulted in the need for newer classes of agents to improve treatment outcomes.[1–3] Maturation inhibitors (MIs) target a viral replication mechanism that is distinct from the existing protease, reverse transcriptase, and integrase inhibitor classes.[2] MIs interfere with one of the final steps of the HIV-1 life cycle to prevent the formation of infectious viral particles, specifically by blocking protease-mediated processing of the structural Gag polyprotein.[4]

GSK3640254 (Figure 1) is an MI being developed for HIV-1 treatment. In vitro studies of GSK3640254 have demonstrated broad-spectrum potent inhibition across various HIV-1 subtypes.[5] In phase I studies in healthy participants (NCT03231943, NCT03575962), GSK3640254 was generally well tolerated, with headache reported as the most common adverse event (AE).[5] Pharmacokinetic analysis showed that GSK3640254 was slowly absorbed, with a median time to maximum observed concentration (t_{max}) of 3.0 hours and an estimated half-life of approximately 22.6 hours for the 200-mg dose, supportive of once-daily dosing.[5] In the phase IIa proof-of-concept study in treatment-naive adults with HIV-1 (NCT03784079), the GSK3640254 200-mg dose resulted in an approximately 2-$\log_{10}$ reduction in plasma HIV-1 RNA with no noted safety or tolerability concerns.[6] GSK3640254 is an inhibitor of uridine diphosphate glucuronosyltransferase 1A1 and

[1] ViiV Healthcare, Research Triangle Park, North Carolina, USA
[2] GlaxoSmithKline, Collegeville, Pennsylvania, USA
[3] ViiV Healthcare, Branford, Connecticut, USA
[4] GlaxoSmithKline, Brentford, UK

Submitted for publication 18 August 2021; accepted 27 October 2021.

Corresponding Author:
Mark Johnson, PhD, ViiV Healthcare, 5 Moore Drive, Research Triangle Park, NC 27709-3398
(e-mail: mark.a.johnson@viivhealthcare.com)

[†] Employee of GlaxoSmithKline during the conduct of the study.

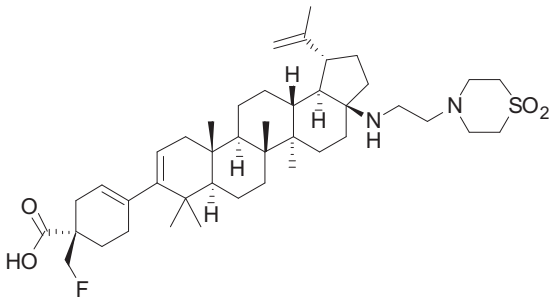

Figure 1. Structure of GSK3640254.

organic anion-transporting polypeptide 1B3 in vitro.[7,8] Drug interaction studies have demonstrated no meaningful effect of GSK3640254 on the pharmacokinetics of dolutegravir, tenofovir alafenamide, or combined oral contraceptives.[7–9]

In both phase I and phase IIa proof-of-concept studies, GSK3640254 was formulated as a mesylate salt in a capsule.[5,6] In planned phase IIb studies, the proposed formulation for GSK3640254 is a mesylate salt in a tablet. Because of the planned formulation change between phase IIa and phase IIb studies, it was critical to determine whether dose adjustments were required. Additionally, as all GSK3640254 completed clinical studies to date have been conducted under moderate-calorie and -fat conditions, it was important to investigate the effect of moderate- and high-fat conditions on the pharmacokinetics and safety of the planned GSK3640254 mesylate tablet formulation in comparison with fasted conditions.

Herein, we report the results from a phase I, 2-part study in healthy participants assessing the relative bioavailability of a single dose of GSK3640254 200 mg in tablet and capsule formulations as well as the effect of food on the pharmacokinetic and safety profile of the tablet formulation.

Methods

Study Design

This was a phase I, 2-part, randomized, open-label, single-dose, crossover study conducted at 1 center in the United States (PPD, Austin, Texas) to compare the relative bioavailability of GSK3640254 mesylate salt tablet and capsule formulations (part 1) and to assess the effect of food on the GSK3640254 tablet formulation (part 2) in healthy adults (ClinicalTrials.gov identifier, NCT04263142). Part 1 consisted of a screening period (≤28 days before day 1 of treatment) and 2 sequential single-dose treatment periods separated by a ≥7-day washout (Figure 2A). Participants were randomized to 1 of 2 GSK3640254 200 mg treatment sequences (capsule-tablet or tablet-capsule). Treatments were administered as a single dose given as two 100-mg capsules or tablets with a moderate-fat meal 30 minutes before dosing. Part 2 consisted of a screening period (≤28 days before day 1 of treatment) and 3 sequential single-dose treatment periods separated by a ≥7-day washout (Figure 2B). Participants were randomized to 1 of 3 treatment sequences with a single dose of GSK3640254 200 mg given as two 100-mg tablets (moderate-fat, fasted, and high-fat conditions) in each treatment period. Participants received either a moderate- or high-fat meal 30 minutes before dosing or fasted overnight for at least 10 hours before dosing and until 4 hours after dosing.

The study was conducted in accordance with the International Conference on Harmonization ethical

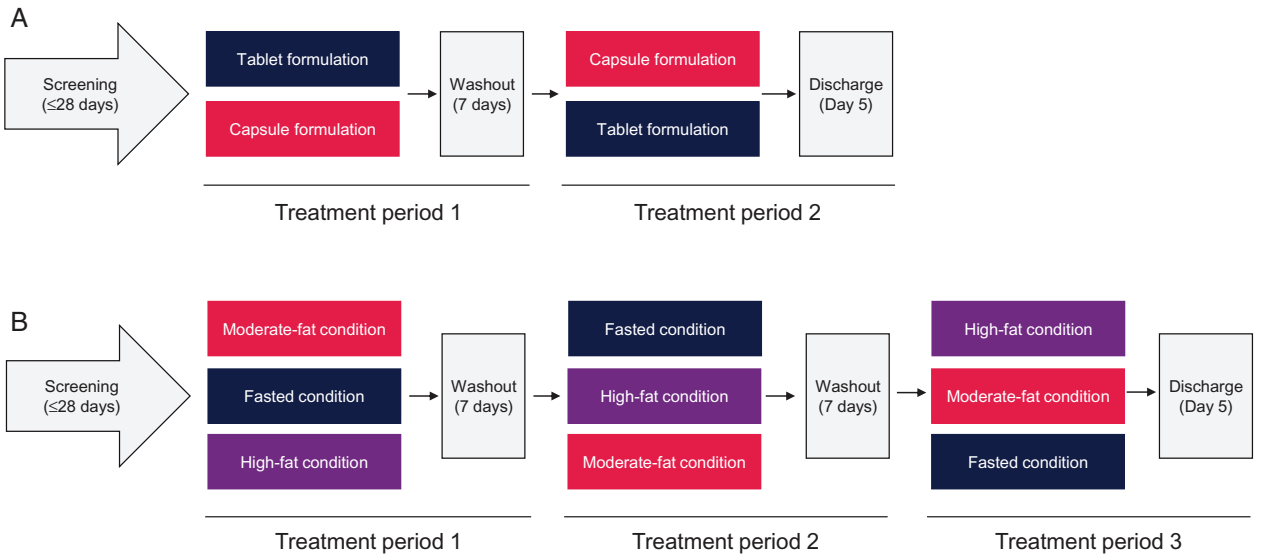

Figure 2. Study design schematics for (A) part 1 and (B) part 2.

Table 1. Baseline Demographics of the Study Populations for Part 1 and Part 2

Parameter	Part 1 (N = 18)	Part 2 (N = 21)
Age, y, mean (SD)	35.8 (9.25)	32.7 (9.01)
Sex, n (%)		
Female	5 (28)	9 (43)
Male	13 (72)	12 (57)
BMI, kg/m^2, mean (SD)	27.2 (2.97)	26.5 (3.51)
Height, cm, mean (SD)	172 (11.7)	170 (10.1)
Weight, kg, mean (SD)	80.8 (16.5)	76.8 (13.7)
Ethnicity, n (%)		
Hispanic or Latino	8 (44)	6 (29)
Not Hispanic or Latino	10 (56)	15 (71)
Race, n (%)		
White	10 (56)	12 (57)
Black or African American	6 (33)	9 (43)
American Indian or Alaskan Native	1 (6)	0
Native Hawaiian or other Pacific Islander	1 (6)	0

BMI, body mass index; SD, standard deviation.

Table 2. Part 1 Summary of GSK3640254 Plasma Pharmacokinetic Parameters by Treatment

Parameter	Capsule 200 mg (N = 18)	Tablet 200 mg (N = 18)
$AUC_{0-\infty}$, μg • h/mL		
Geometric mean (%CVb)	36.9 (42.7)	36.9 (40.3)
Arithmetic mean (SD)	39.6 (13.9)	39.4 (13.9)
AUC_{0-t}, μg • h/mL		
Geometric mean (%CVb)	33.7 (41.1)	33.8 (40.2)
Arithmetic mean (SD)	35.9 (11.8)	36.1 (12.5)
C_{max}, μg/mL		
Geometric mean (%CVb)	1.20 (33.4)	1.31 (45.3)
Arithmetic mean (SD)	1.26 (0.369)	1.43 (0.577)
t_{max}, h		
Median (range)	5.00 (3.00-12.0)	4.00 (2.50-6.00)
$t_{1/2}$, h		
Geometric mean (%CVb)	26.2 (17.6)	26.2 (17.2)
Arithmetic mean (SD)	26.6 (4.68)	26.5 (4.59)
CL/F		
Geometric mean (%CVb)	5.41 (42.7)	5.42 (40.3)
Arithmetic mean (SD)	5.94 (3.23)	5.84 (2.45)

$AUC_{0-\infty}$, area under the plasma concentration–time curve from time 0 extrapolated to infinity; AUC_{0-t}, area under the plasma concentration–time curve from time 0 to last quantifiable concentration; CL/F, apparent oral clearance; C_{max}, maximum observed concentration; CVb, between-participant coefficient of variation; SD, standard deviation; $t_{1/2}$, apparent terminal phase half-life; t_{max}, time to C_{max}.

principles of good clinical practice and the Declaration of Helsinki. Written informed consent was obtained from each participant. The protocol and study conduct were approved by an institutional review board (IntegReview IRB, Austin, Texas).

Study Participants

Eligible participants were generally healthy individuals aged 18 to 55 years, and eligible female participants could not be pregnant (confirmed by a negative highly sensitive serum pregnancy test at screening) or able to become pregnant (using a nonhormonal contraceptive method). Additional eligibility criteria included body weight ≥50 kg (men) and ≥45 kg (women), and body mass index between 18.5 and 31.0 kg/m^2. Participants were excluded from the study if they had a history of any condition that could affect the absorption, metabolism, or excretion of the study treatment or a history of liver or cardiac disease. Additional exclusion criteria were related to laboratory parameters, including a positive HIV, hepatitis B, or hepatitis C test or alanine aminotransferase >1.5 times the upper limit of normal.

Study Assessments

The primary objective of part 1 was to assess the relative bioavailability of GSK3640254 mesylate tablets and capsules in the presence of a moderate-fat meal using pharmacokinetic parameters. The primary objective of part 2 was to assess the effect of food on the pharmacokinetics of the tablet formulation. Secondary objectives were to assess the safety and tolerability of GSK3640254 after single oral administration and to characterize pharmacokinetics.

In both parts 1 and 2, blood samples for pharmacokinetic analysis were collected 40 minutes before dosing on day 1 and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 72, and 96 hours after dosing in each treatment period. GSK3640254 concentrations were measured using ultra-high-performance liquid chromatography with tandem mass spectrometry.[8] Safety and tolerability were assessed by monitoring and recording AEs, clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram results, and physical examination findings.

Data Analysis

No formal statistical hypotheses were tested in this study. The sample size calculation was based on a 38% intraparticipant coefficient of variation based on the results from previous pharmacokinetic studies of GSK3640254. Plasma concentrations were summarized descriptively. Pharmacokinetic parameters were calculated by standard noncompartmental methods using Phoenix WinNonlin version 8.0 (Certara, Princeton, New Jersey), based on actual sampling times. Primary plasma pharmacokinetic parameters (area under the plasma concentration–time curve from time 0 extrapolated to infinity [$AUC_{0-\infty}$], area under the plasma

Table 3. Part 1 Statistical Analysis of GSK3640254 Pharmacokinetic Parameters: Analysis of Variance[a]

Parameter	Geometric LS Mean	Ratio	90%CI	Intraparticipant CV
$AUC_{0-\infty}$, μg • h/mL				
Capsule (n = 18)	36.9	0.998	0.926 to 1.08	12.9
Tablet (n = 18)	36.9			
AUC_{0-t}, μg • h/mL				
Capsule (n = 18)	33.7	1.00	0.932 to 1.08	12.5
Tablet (n = 18)	33.8			
C_{max}, μg/mL				
Capsule (n = 18)	1.20	1.09	0.989 to 1.21	17.4
Tablet (n = 18)	1.31			
t_{max}, h				
Capsule (n = 18)	5.00[b]	−1.28[c]	−2.00 to −0.283	–
Tablet (n = 18)	4.00[b]			

$AUC_{0-\infty}$, area under the plasma concentration–time curve from time 0 extrapolated to infinity; AUC_{0-t}, area under the plasma concentration–time curve from time 0 to last quantifiable concentration; C_{max}, maximum observed concentration; CV, coefficient of variation; LS, least squares; t_{max}, time to C_{max}.
[a] An analysis of variance with treatment, period, and sequence as fixed effects and participant as a random effect was performed on the natural ln-transformed parameters $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}.
[b] Median.
[c] Median difference.

Table 4. Part 2 Summary of GSK3640254 Plasma Pharmacokinetic Parameters by Treatment

Parameter	Moderate Fat (N = 20)	Fasted (N = 19)[a]	High Fat (N = 21)
$AUC_{0-\infty}$, μg • h/mL[b]			
Geometric mean (%CVb)	41.0 (42.2)	13.5 (58.2)	36.9 (35.9)
Arithmetic mean (SD)	44.1 (16.3)	15.7 (10.9)	39.1 (13.6)
AUC_{0-t}, μg • h/mL[c]			
Geometric mean (%CVb)	37.9 (41.5)	11.4 (65.6)	34.1 (34.9)
Arithmetic mean (SD)	40.7 (15.0)	13.5 (9.5)	36.0 (11.9)
C_{max}, μg/mL[c]			
Geometric mean (%CVb)	1.43 (35.6)	0.354 (84.4)	1.08 (38.6)
Arithmetic mean (SD)	1.51 (0.512)	0.449 (0.351)	1.16 (0.434)
t_{max} (hour)[c]			
Median (range)	5.00 (2.00–8.00)	4.00 (2.03–24.0)	5.00 (1.50–12.0)
$t_{1/2}$ (hour)[b]			
Geometric mean (%CVb)	24.9 (18.0)	25.7 (12.7)	24.8 (15.7)
Arithmetic mean (SD)	25.3 (5.13)	25.9 (3.33)	25.1 (4.18)
CL/F[b]			
Geometric mean (%CVb)	4.88 (42.2)	14.9 (58.2)	5.42 (35.9)
Arithmetic mean (SD)	5.30 (2.37)	16.6 (7.44)	5.74 (2.01)

$AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{0-t}, area under the plasma concentration–time curve from time 0 to last quantifiable concentration; CL/F, apparent oral clearance; C_{max}, maximum observed concentration; CVb, between-participant coefficient of variation; SD, standard deviation; $t_{1/2}$, apparent terminal phase half-life; t_{max}, time of C_{max}.
[a] Six participants who received GSK3640254 under fasted conditions had predose plasma concentrations >5% of C_{max}; these participants were excluded from summary statistics and statistical analyses.
[b] n = 10, fasted condition.
[c] n = 13, fasted condition.

concentration–time curve from time 0 to the last quantifiable concentration [AUC_{0-t}], maximum observed concentration [C_{max}], and t_{max}) and secondary plasma pharmacokinetic parameters (apparent terminal phase half-life [$t_{1/2}$] and apparent oral clearance [CL/F]) were estimated for GSK3640254. Statistics were summarized by treatment for each part of the study. Analyses to compare the relative bioavailability of the tablet formulation of GSK3640254 with the capsule formulation were performed on the natural logarithms of pharmacokinetic parameters $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} using linear mixed-effect models with treatment, period, and sequence as fixed effects and participant as a random effect. Effects were estimated, and CIs were obtained

Table 5. Part 2 Statistical Analysis of GSK3640254 Pharmacokinetic Parameters: Analysis of Variance[a]

Parameter	Geometric LS Mean	Ratio[b]	90%CI	Intraparticipant CV
$AUC_{0-\infty}$, μg • h/mL				
Fasted (n = 19)[c,d]	14.2	–	–	27.5
Moderate fat (n = 20)	41.6	2.93	2.37 to 3.61	
High fat (n = 21)	36.9	2.59	2.10 to 3.20	
AUC_{0-t}, μg • h/mL				
Fasted (n = 19)[c,e]	12.2	–	–	29.5
Moderate fat (n = 20)	38.5	3.15	2.59 to 3.82	
High fat (n = 21)	34.1	2.79	2.29 to 3.38	
C_{max}, μg/mL				
Fasted (n = 19)[c,e]	0.351	–	–	36.1
Moderate fat (n = 20)	1.44	4.10	3.24 to 5.18	
High fat (n = 21)	1.08	3.08	2.44 to 3.89	
t_{max}, h[f]				
Fasted (n = 19)[c]	4.00[g]	–	–	–
Moderate fat (n = 20)	5.00[g]	0.500[h]	−0.750 to 1.98	
High fat (n = 21)	5.00[g]	1.50[h]	0.250 to 2.75	

$AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to last quantifiable concentration; C_{max}, maximum observed concentration; CV, coefficient of variation; LS, least squares; t_{max}, time to C_{max}.

[a] An analysis of variance with treatment, period, and sequence as fixed effects and participant as a random effect was performed on the natural ln-transformed parameters $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}.

[b] Ratio compared with fasted conditions.

[c] Six participants who received GSK3640254 under fasted conditions had predose plasma concentrations >5% of C_{max}; these participants were excluded from summary statistics and statistical analyses.

[d] n = 10, fasted condition.

[e] n = 13, fasted condition.

[f] n = 13, all conditions.

[g] Median.

[h] Median difference.

for the tablet vs the capsule. Nonparametric analysis was performed to compare the t_{max} of the tablet formulation with the capsule formulation, and the Hodges-Lehmann estimate was used to produce the treatment difference. For the food effect, the same mixed-effects model was evaluated with fixed-effects terms for treatment (fasted, moderate fat, and high fat), period, and sequence and participant as a random effect. The effect of food on the t_{max} of the tablet formulation was similarly analyzed for moderate-fat vs fasted and high-fat vs fasted conditions. Safety analyses were based on the safety population, defined as all participants who received ≥1 dose of study medication, and were summarized descriptively.

Results

Study Population

Across both studies, 94 participants were screened, and 39 participants (41%) were enrolled. In part 1, 18 participants (men, n = 13; women, n = 5) with a mean (SD) age of 35.8 (9.25) years were randomized to treatment, all of whom completed the study. In part 2, 21 participants (men, n = 12; women, n = 9) with a mean (SD) age of 32.7 (9.01) years were randomized to treatment, 19 (90%) of whom completed the study. One participant (5%) was withdrawn because of an AE, and 1 (5%) was withdrawn as a result of physician's decision. Baseline demographics from participants in parts 1 and 2 are summarized in Table 1.

Pharmacokinetic Results

In part 1, mean peak (C_{max}) and total ($AUC_{0-\infty}$ and AUC_{0-t}) plasma exposures after administration of the GSK3640254 tablet formulation were not meaningfully different compared with the capsule formulation in the presence of a moderate-fat meal (Figure 3). Pharmacokinetic data from the summary statistics and analysis of variance models for part 1 are shown in Tables 2 and 3, respectively. With both formulations, plasma concentrations declined in a monophasic manner. Geometric least squares (LS) mean ratios between the formulations were 0.998, 1.00, and 1.09 for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}, respectively. The median (90%CI) difference in t_{max} for the tablet formulation compared with the capsule formulation was −1.28 hours (−2.00 to −0.283). Mean estimates for $t_{1/2}$ and CL/F were similar for both formulations.

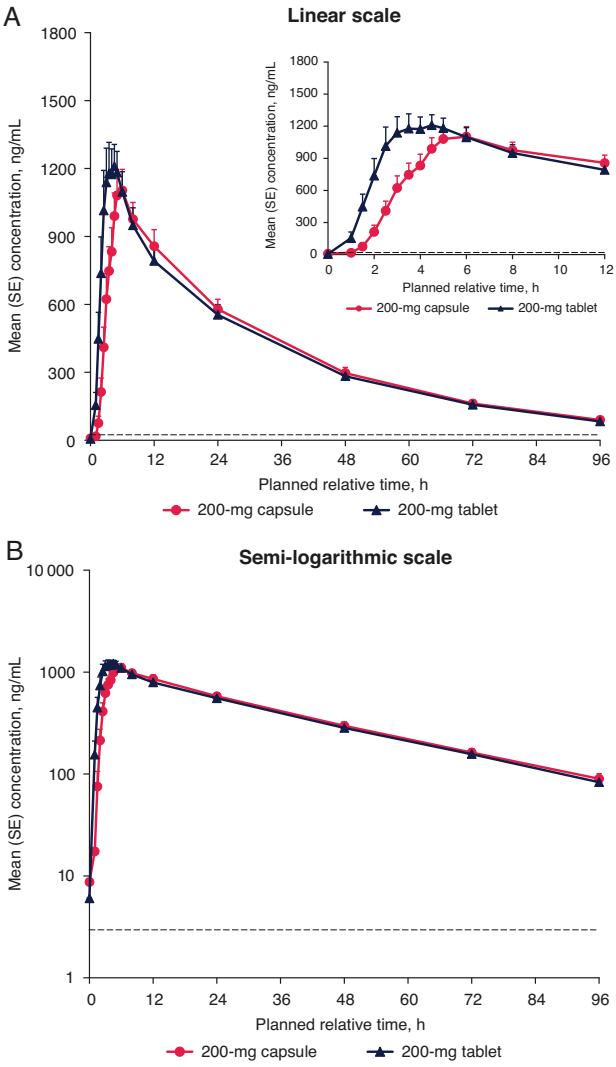

Figure 3. Mean (SD) GSK3640254 plasma concentration–time plots by treatment in part 1: (A) linear and (B) semilogarithmic. Dashed line represents lower limit of quantification (3.00 ng/mL). SE, standard error.

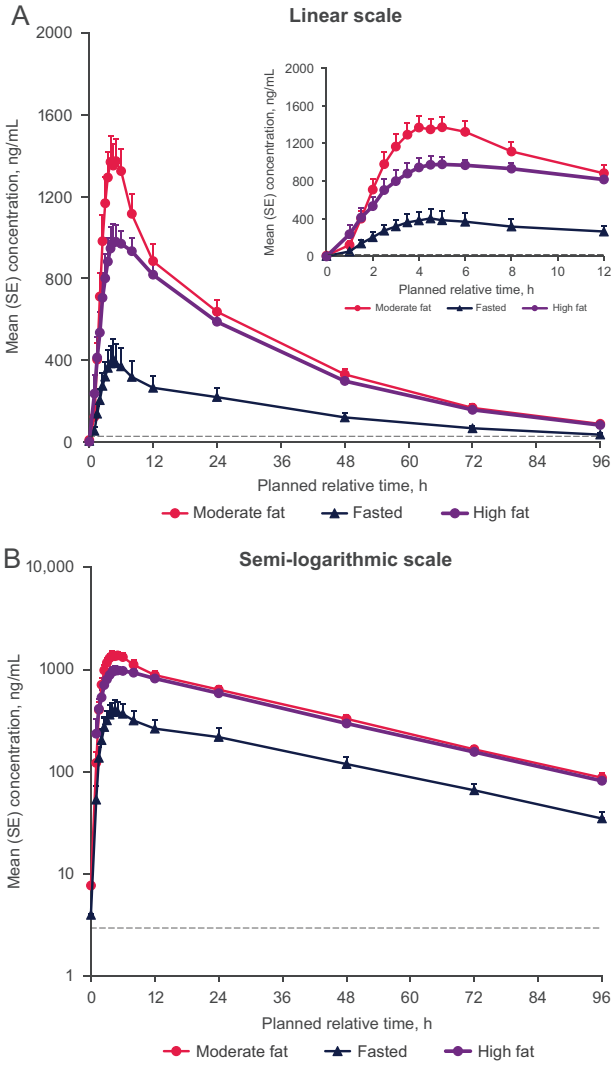

Figure 4. Mean (SD) GSK3640254 plasma concentration–time plots by treatment in part 2: (A) linear and (B) semilogarithmic. Dashed line represents lower limit of quantification (3.00 ng/mL).

In part 2, when the GSK3640254 tablet formulation was administered in the presence of a moderate- or high-fat meal, mean peak (C_{max}) and total ($AUC_{0-\infty}$ and AUC_{0-t}), plasma exposures were higher than under fasted conditions (Figure 4). Pharmacokinetic data from the summary statistics and analysis of variance models for part 2 are shown in Tables 4 and 5, respectively. Six participants who received GSK3640254 under fasted conditions had predose plasma concentrations >5% of the C_{max} value for the treatment and were excluded from summary statistics and mean concentration-time plots. Mean C_{max} values under moderate- and high-fat conditions were ≈4- and 3-fold higher, respectively, than under fasted conditions. Moderate- and high-fat conditions increased mean $AUC_{0-\infty}$ by ≈3.1- and 2.7-fold, respectively, compared with fasted conditions. Geometric LS mean ratios between moderate-fat and fasted conditions were 2.93, 3.15, and 4.10 for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}, respectively. Comparing high-fat and fasted conditions, geometric LS mean ratios were 2.59, 2.79, and 3.08 for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max}, respectively. For all treatment conditions, plasma concentrations declined in a monophasic manner. Median (90%CI) difference in t_{max} was 0.500 (−0.750 to 1.98) and 1.50 hours (0.250 to 2.75) for the moderate- and high-fat conditions, respectively, compared with the fasted condition. Mean estimates for $t_{1/2}$ were similar across treatment conditions, while the mean estimate for CL/F was >60% lower under moderate- or high-fat conditions than under fasted conditions.

Table 6. Summary of All Adverse Events

Preferred Term, n (%)	Part 1		Part 2		
	Capsule 200 mg (N = 18)	Tablet 200 mg (N = 18)	Moderate Fat (N = 20)	Fasted (N = 19)	High Fat (N = 21)
Any event	0	1 (6)	0	0	5 (24)
Eye disorders					
Eye irritation	0	1 (6)	0	0	0
Gastrointestinal disorders					
Diarrhea[a]	0	0	0	0	2 (10)
Abdominal distention[a]	0	0	0	0	1 (5)
Psychiatric disorders					
Anxiety	0	0	0	0	1 (5)
Reproductive system and breast disorders					
Dysmenorrhea	0	0	0	0	1 (5)
Skin and subcutaneous tissue disorders					
Rash maculopapular[a,b]	0	0	0	0	1 (5)

At each level of participant summarization, a participant was counted once if the participant reported ≥1 events. Adverse events that occurred after last treatment date and time + 5 days were not included.
[a] Drug related.
[b] Led to participant withdrawal from study.

Safety Results

In part 1, 1 (6%) participant experienced an AE of mild eye irritation after administration of the GSK3640254 tablet formulation (Table 6). This event was assessed as not related to the study treatment by the investigator. No AEs were reported after administration of the GSK3640254 capsule formulation.

In part 2, 5 (24%) participants experienced AEs, all of which occurred after administration of GSK3640254 tablets under high-fat conditions. All AEs were considered mild. The most commonly reported AE was diarrhea (n = 2; 10%). Two (10%) participants reported 3 AEs that were considered related to the study treatment: 1 participant experienced abdominal distention (resolved 2 hours after onset) and diarrhea (resolved 1 minute after onset), and the other participant experienced an AE of rash maculopapular, leading to withdrawal from the study. The event was resolved ≈11 days after onset. There were no serious AEs or clinically relevant trends in laboratory values, vital sign measurements, or electrocardiograms reported in part 1 or 2 of the study.

Discussion

In this phase I, 2-part trial, the relative bioavailability of the GSK3640254 capsule and tablet formulations and the effect of food on GSK3640254 pharmacokinetics were evaluated in healthy participants. Results demonstrated that the tablet formulation of GSK3640254 planned for the phase IIb study was comparable to the capsule formulation used in prior phase I and phase IIa clinical studies, with no noted safety or tolerability findings.

After administration of a single dose of GSK3640254 200 mg under moderate-fat conditions, mean peak and total plasma exposures were similar between the capsule and tablet formulations (geometric mean ratios between 0.998 and 1.09), indicating good relative bioavailability.

A food effect was expected given the structural similarity to a prior MI that also needed administration with food to achieve adequate exposure.[3] Relative to the fasted state, concomitant intake of food with oral drug formulations can significantly affect the rate and extent of drug absorption and bioavailability.[10] Such variations in drug exposures are generally due to food-mediated changes in physiological processes such as fluctuations in gastrointestinal pH, increase in luminal fluids, release of bile salts, increase in splanchnic blood flow, and inhibition of transporters.[10–12] Compared with administration under fasted conditions, administration of GSK3640254 under high- and moderate-fat conditions resulted in a 3- to 4-fold increase in mean peak and total plasma exposures (geometric mean ratios between 2.59 and 4.10). This increase in plasma exposure with the coadministration of food is similar to observations from another MI study.[13] Relative to fasted conditions, increases in peak (C_{max}) and total ($AUC_{0-\infty}$ and AUC_{0-t}) plasma exposures appeared to be greater under moderate-fat conditions (geometric mean ratios between 2.93 and 4.10) than high-fat conditions (geometric mean ratios between 2.59 and 3.08). However, this study was not specifically designed to compare

increases in exposures between moderate- and high-fat meals. Moderate- and high-fat conditions slightly delayed t_{max} relative to fasted conditions (median difference of 0.500 and 1.50 hours, respectively). Median t_{max} values for GSK3640254 were similar regardless of formulation or meal content (4-5 hours).

A potential limitation of this study is the reduced precision in the statistics from part 2 due to the exclusion of participants from the fasted treatment group with predose plasma concentrations >5% of the C_{max} value for the treatment.

Overall, the results from this study confirmed the suitability of the GSK3640254 tablet formulation for the phase IIb study (NCT04493216).

Acknowledgments

This study was funded by ViiV Healthcare. Editorial assistance was provided under the direction of the authors by Bethany Reinecke, PhD, and Jennifer Rossi, MA, ELS, MedThink SciCom.

Conflicts of Interest

M.J., S.R.J., and M.L. are employees of ViiV Healthcare and may own stock in GlaxoSmithKline (GSK). A.M., V.B., and J.Z. are employees of and may own stock in GSK. T.P.D. was an employee of GSK during the conduct of the study and may own stock in GSK.

Funding

This study was funded by ViiV Healthcare.

References

1. Cihlar T, Fordyce M. Current status and prospects of HIV treatment. *Curr Opin Virol*. 2016;18:50-56.
2. Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. *Cold Spring Harb Perspect Med*. 2012;2(4):a007161.
3. Morales-Ramirez J, Bogner JR, Molina J-M, et al. Safety, efficacy, and dose response of the maturation inhibitor GSK3532795 (formerly known as BMS-955176) plus tenofovir/emtricitabine once daily in treatment-naive HIV-1-infected adults: week 24 primary analysis from a randomized phase IIb trial. *PLoS One*. 2018;13(10):e0205368.
4. Wang D, Lu W, Li F. Pharmacological intervention of HIV-1 maturation. *Acta Pharm Sin B*. 2015;5(6):493-499.
5. Joshi SR, Fernando D, Igwe S, et al. Phase I evaluation of the safety, tolerability, and pharmacokinetics of GSK3640254, a next-generation HIV-1 maturation inhibitor. *Pharmacol Res Perspect*. 2020;8(6):e00671.
6. Spinner C, Felizarta F & Rizzardini G et al; 208132 Study Team. Phase IIa proof-of-concept trial of next-generation maturation inhibitor GSK3640254. Slides presented at Conference on Retroviruses and Opportunistic Infections, March 6-10, 2021.
7. 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. *Br J Clin Pharmacol*. 2021;87(9):3501-3507.
8. Pene Dumitrescu T, Joshi SR, Xu J, et al. A phase I evaluation of the pharmacokinetics and tolerability of the HIV-1 maturation inhibitor GSK3640254 and tenofovir alafenamide/emtricitabine in healthy participants. *Antimicrob Agents Chemother*. 2021;65(6):e02173-20.
9. Pene Dumitrescu T, Greene TJ, Joshi SR, et al. Lack of pharmacokinetic interaction between the HIV-1 maturation inhibitor GSK3640254 and combination oral contraceptives in healthy women. *Br J Clin Pharmacol*. 2022;88:1704-1712.
10. O'Shea JP, Holm R, O'Driscoll CM, Griffin BT. Food for thought: formulating away the food effect – a PEARRL review. *J Pharm Pharmacol*. 2019;71(4):510-535.
11. Koziolek M, Alcaro S, Augustijns P, et al. The mechanisms of pharmacokinetic food-drug interactions—a perspective from the UNGAP group. *Eur J Pharm Sci*. 2019;134:31-59.
12. Cheng L, Wong H. Food effects on oral drug absorption: application of physiologically-based pharmacokinetic modeling as a predictive tool. *Pharmaceutics*. 2020;12(7):672.
13. Johnson M, Jewell RC, Gan J, Dumont E, Burns O, Johns BA. A phase 1 study to assess the relative bioavailability, food effect, and safety of a tablet formulation of GSK2838232, a novel HIV maturation inhibitor in healthy participants after single and repeated doses. *Clin Pharmacol Drug Dev*. 2020;9(8):972-977.