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ORIGINAL ARTICLE

Phase I evaluation of the safety, tolerability, and pharmacokinetics of GSK3640254, a next-generation HIV-1 maturation inhibitor

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Abstract

Despite advances in HIV-1 management with antiretroviral therapy, drug resistance and toxicities with multidrug regimens can result in treatment failure. Hence, there is a continuing demand for antiretroviral agents (ARVs) with novel mechanisms of action. Maturation inhibitors inhibit HIV-1 replication via a unique mechanism of action and can be combined with other ARVs. Two phase I randomized clinical trials were conducted for a maturation inhibitor, GSK3640254, to determine safety, pharmacokinetics (NCT03231943), and relative bioavailability (NCT03575962) in healthy adults. The first trial was conducted in two parts. Part 1 was conducted in a two-cohort, interlocking, eight-period fashion in 20 participants with single ascending doses of GSK3640254 (1-700 mg) or placebo. In Part 2, 58 participants were randomized to receive GSK3640254 (n = 44) or placebo (n = 14). Four participants reported adverse events (AEs) leading to study discontinuation, with one adverse drug reaction (maculopapular rash). There was no relationship between frequency or severity of AEs and dose. Pharmacokinetic assessments showed that GSK3640254 was slowly absorbed, with time to maximum concentration (tmax) occurring between 3.5 and 4 hours and half-life of ~24 hours. In the relative bioavailability study of GSK3640254 mesylate salt vs bis-hydrochloride salt capsules in 14 healthy adults, the mesylate salt performed slightly better than the bis-hydrochloride formulation (12%-16% increase in area under the concentration-time curve and maximum concentration); tmax (5 hours) was similar between the formulations. Initial pharmacokinetic and safety data from these healthy-participant studies informed further development of GSK3640254 for once-daily dosing for the treatment of HIV-1 infection.

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; FTIH, first-time-in-human; MI, maturation inhibitor.

KEYWORDS
bioavailability, clinical study, first-time-in-human, healthy participants, HIV-1 infection, pharmacokinetics, safety

1 | INTRODUCTION

Current antiretroviral therapy (ART) regimens typically target the reverse transcriptase, protease, or integrase proteins of HIV. However, drug resistance and toxicities associated with ART can result in treatment failure.[1] Therefore, there continues to be an unmet need for newer classes of antiretroviral agents (ARVs) that target other steps in the viral life cycle, particularly for treatment-experienced individuals with acquired drug-resistant forms of HIV.

Maturation, which is near the final phase in the viral life cycle, offers a new therapeutic avenue for intervention.[1] Maturation refers to the step that is catalyzed by the viral protease, wherein the Gag polyprotein is cleaved into its component proteins. This leads to virion core condensation and is essential for the formation of infectious virus particles. A new class of drugs termed maturation inhibitors (MIs) target the HIV structural protein (Gag) and inhibit viral maturation by inhibiting protease-mediated cleavage of CA-SP1 in the Gag polyprotein. Pharmacologic inhibition of maturation has shown inhibition of replication of HIV-1 isolates in vitro and in several phase IIa clinical trials; in one phase IIb clinical trial, inhibition of maturation in combination with two nucleoside reverse transcriptase inhibitors has shown therapeutic benefit.[1-5] GSK3640254 is a next-generation MI that has demonstrated broad-spectrum inhibition across various HIV-1 subtypes. Here, we report the safety, tolerability, and pharmacokinetic (PK) findings from the first two phase I clinical trials of GSK3640254 in healthy participants, showing that it is generally well-tolerated and suitable for further evaluation in a phase IIa study.

2 | MATERIALS AND METHODS

We conducted two clinical studies of the MI GSK3640254 in healthy participants. The first study (ClinicalTrials.gov identifier, NCT03231943) was a first-time-in-human (FTIH), double-blind (Sponsor unblinded), randomized, placebo-controlled, single and multiple ascending dose study to investigate the safety, tolerability, and PK of GSK3640254. The second study (ClinicalTrials.gov identifier, NCT03575962) was a single-center, two-period, open-label relative bioavailability study of the mesylate salt formulation of GSK3640254 compared with the bis-hydrochloride salt formulation. The mesylate salt of GSK3640254 provided superior solid-state stability, much lower moisture uptake, better thermal behavior, an absence of hard agglomerates requiring size reduction, and improved solubility compared with the bis-hydrochloride salt of this active pharmaceutical ingredient. Both studies were designed in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice, following the principles of the Declaration of Helsinki. South West-Central Bristol Research Ethics Committee (single ascending dose/multiple ascending dose study; Bristol, UK) and Health and Care Research Wales (relative bioavailability study; Cardiff, UK) approved the research protocols.

2.1 | Study participants

Healthy women of nonchildbearing potential and healthy men between 18 and 55 years of age with body mass index (BMI) between 18.5 and 32.0 kg/m^2 (19.0-32.0 kg/m^2 for the relative bioavailability study) were eligible for inclusion. Participants were excluded if they had a positive HIV, hepatitis B, or hepatitis C test; a history of liver or cardiac disease; alanine aminotransferase (ALT) >1.5 times the upper limit of normal; or any conditions that could affect the absorption, distribution, metabolism, or excretion of the investigational drug. All participants provided written informed consent before initiation of study procedures, and the trials were conducted in accordance with the International Council on Harmonisation guidelines and ethical principles outlined in the Declaration of Helsinki.

2.2 | Study design

2.2.1 | Single (Part 1) and multiple ascending dose (Part 2) FTIH study

This study was performed in two parts (Figure 1). Part 1 (n = 16 planned) was conducted in an interlocking fashion using a two-cohort crossover design over four periods, with eight participants planned per cohort. Participants were randomized 3:1 (GSK3640254 to placebo) so that six participants received a single oral dose of GSK3640254 (1-700 mg) and two received placebo in each study period (Figure S1). In Part 1, two participants within each period served as sentinel participants; the remaining six participants in each period could not be dosed until the 24-hour safety data for the first two participants had been reviewed. Participants in cohorts 1 and 2 received three ascending doses of GSK3640254 and one placebo dose in a crossover manner, except in cases of early withdrawals or discontinuations. Recruitment of additional participants was allowed to replace those who withdrew or discontinued early. The starting dose in Part 1 was 1 mg. This starting dose was lower than that calculated based on the no observed adverse effect level (NOAEL) in rats of 10 mg/kg (maximum recommended starting dose [MRSD], approximately 9.6 mg) and the lowest observed adverse effect level

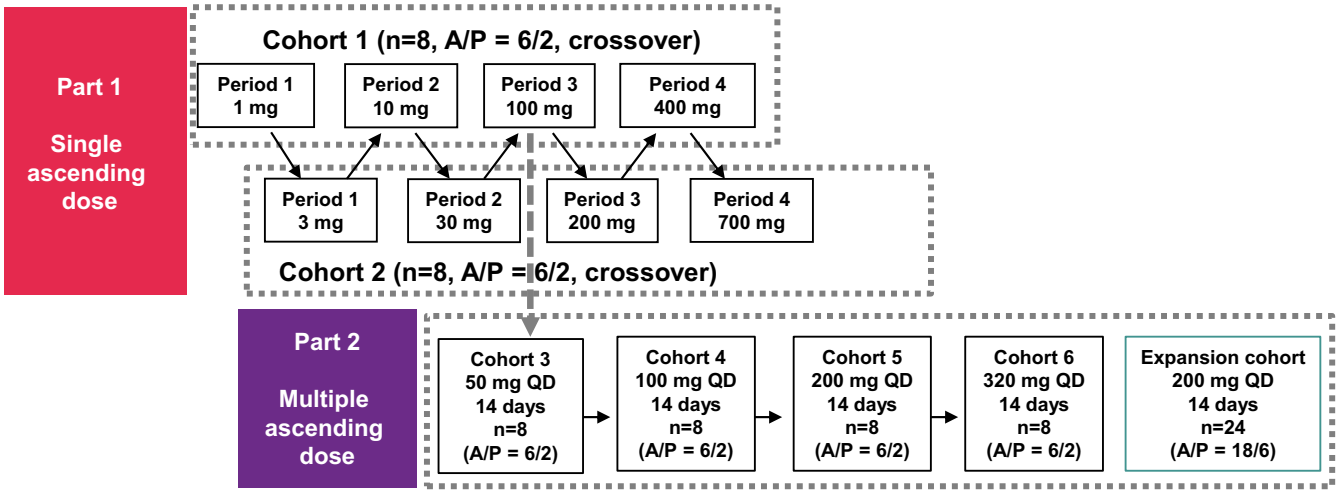

FIGURE 1 Original study design of the single and multiple ascending dose study. A/P, active treatment/placebo; QD, once daily. Cohort 1 required four replacement participants to undergo randomization to complete the remainder of the periods. Cohort 6 and the expansion cohort required one replacement participant each to undergo randomization and complete the treatment period

in dogs of 1 mg/kg (MRSD, approximately 3.2 mg), in the absence of a NOAEL in dogs. Pharmacokinetic-based dose escalation would stop in Part 1 if the Bayesian predicted probability was >50% that the subsequent dose would result in any participant having a maximum concentration (Cmax) exceeding 7.96 μg/mL, a concentration that led to minimal QT effects in one dog administered a single dose of 17 mg/kg; this may have occurred with a maximum dose >700 mg.

Part 2 (n = 56 planned) was conducted once the 100-mg single-dose safety and PK results from Part 1 were available. The study was designed to include four cohorts with eight participants per cohort, who were randomized to receive once-daily doses of GSK3640254 (50, 100, 200, or 320 mg) or placebo for 14 days (six received GSK3640254 and two received placebo at each dose level). In Part 2, 24 participants were planned for inclusion in an expansion cohort to further evaluate gastrointestinal (GI) intolerability observed with a structurally similar prior generation MI; this occurred after the safety and PK data from cohorts 3 to 5 (50, 100, and 200 mg) were available. Further evaluation of GI intolerability was planned because of the GI intolerability (predominantly abdominal pain and diarrhea) seen in a prior terminated phase IIb clinical trial investigating a structurally similar MI candidate, GSK3532795.[3] All doses in both parts were administered after a moderate-fat meal (approximately 600 calories with approximately 30% of calories from fat). The starting dose in Part 2 was predefined as being approximately half the likely minimally effective dose; based upon clinical PK data collected in the early doses of Part 1, this was later determined to be 50 mg. Dose escalation would stop in Part 2 if the Bayesian predicted probability was >50% that the subsequent dose would result in any participant exceeding area under the concentration-time curve ($AUC_{0-\tau}$) of 61.1 μg·h/mL at Day 14; this may have occurred with a maximum dose >320 mg.

For both Parts 1 and 2, clinical stopping criteria were met if any of the following occurred: two participants in the same period (Part 1) or cohort (Part 2) experienced a grade 3 adverse drug reaction (ie, drug-related adverse event [AE]); one participant experienced a grade 4 adverse drug reaction; >25% of participants in the same period or cohort experienced a grade ≥3 AE or laboratory abnormality or grade ≥2 rash with concurrent fever, transaminase elevation, or eosinophilia; one participant experienced a serious adverse drug reaction or death that was assessed as an adverse drug reaction; two participants in the same period or cohort had confirmed QTcF ≥500 msec; or two participants in the same period or cohort had clinically significant arrhythmias, as determined by the study investigator.

To determine whether dose escalation could continue, the study team physicians, statisticians, and clinical PK staff from the sponsor had access to data, including but not limited to AEs, vital signs, laboratory findings, electrocardiogram (ECG) parameters, and PK data, which were used to make the dose escalation decision. A review of these data resulted in making dose-escalation decisions for the subsequent period or cohort.

2.2.2 | Relative bioavailability study

Participants (n = 14 planned) were randomized to receive single 200-mg doses of either mesylate salt or bis-hydrochloride salt formulations of GSK3640254 and a single 200-mg dose of the other formulation after a minimum washout period of 7 days. Doses were administered after a moderate-fat meal (approximately 600 calories with approximately 30% of calories from fat).

2.3 | Study assessments

2.3.1 | Single and multiple ascending dose FTIH study

The primary endpoint was to determine the safety and tolerability of GSK3640254 after single and repeated daily administration.

TABLE 1 Demographics and Baseline Characteristics

Parameter	Ascending dose study (NCT03231943)						Bioavailability study (NCT03575962)
	Single-dose part	Multiple-dose part					
	(N = 20)	50 mg (N = 6)	100 mg (N = 6)	200 mg† (N = 25)	320 mg (N = 7)	Placebo (N = 14)	(N = 14)
Age, mean (SD), y	38.8 (9.6)	34.5 (6.4)	42.2 (11.1)	36.9 (8.8)	34.1 (9.7)	35.3 (9.9)	33.9 (12.1)
Gender, male, n (%)	20 (100)	6 (100)	6 (100)	25 (100)	7 (100)	14 (100)	14 (100)
BMI, mean (SD), kg/m^2	25.9 (2.9)	27.6 (2.9)	27.5 (2.1)	25.1 (3.0)	25.5 (2.8)	23.6 (2.7)	25.4 (2.8)
Height, mean (SD), cm	176.8 (6.0)	181.7 (7.1)	174.5 (4.6)	177.2 (6.2)	175.7 (5.1)	178.2 (8.0)	177.1 (6.9)
Weight, mean (SD), kg	80.9 (12.0)	90.0 (11.2)	83.7 (6.9)	79.0 (11.4)	78.5 (9.1)	75.0 (10.5)	79.6 (9.6)

Abbreviations: BMI, body mass index; SD, standard deviation.
†Includes participants from cohort 5 and the expansion cohort.

Secondary endpoints were to describe the PK, examine dose proportionality after single and repeated daily administration, and assess time to steady state of GSK3640254. Plasma was derived from approximately 2 mL of whole blood, and GSK3640254 concentrations were measured using high-performance liquid chromatography with tandem mass spectrometry. Pharmacokinetic parameters were calculated using standard noncompartmental analysis with Phoenix WinNonlin 8 (Certara LP, St Louis, MO). The following parameters were computed: Cmax, time to Cmax (tmax), AUC ($AUC_{0-\infty}$, AUC_{0-24}, $AUC_{0-\tau}$), and terminal-phase half-life. In Part 2, accumulation ratios were also calculated by comparing Cmax, minimum concentration (Ctrough), and $AUC_{0-\tau}$ on Day 14 vs Day 1. Ctrough values up to Day 15 were used for assessment of time to steady state, while dose proportionality was evaluated on Day 1 and Day 15 based on Cmax and AUC values.

2.3.2 | Relative bioavailability study

The primary endpoint of this study was to determine the PK properties of GSK3640254 using noncompartmental analysis after administration of the mesylate salt capsule relative to the bis-hydrochloride salt capsule. Secondary endpoints were analyses related to safety and tolerability.

2.4 | Safety assessments

Safety assessments included monitoring of AEs, physical examinations, vital signs, ECGs, clinical laboratory tests, suicidal risk monitoring, and evaluation of GI and hepatobiliary abnormalities. All AE data were summarized and sorted by system organ class and preferred term assigned by MedDRA version 21.0.

2.5 | Data analyses

For the FTIH single and multiple ascending dose study (Parts 1 and 2), no formal statistical hypothesis was tested. Sample size was based on feasibility. A sample size of eight participants per dose cohort was deemed sufficient to account for the intra- and inter-participant variability to test safety and estimate PK parameters. Pharmacokinetic parameters, including statistical determination of Ctrough, were calculated by standard noncompartmental analysis according to GlaxoSmithKline reporting standards and using Phoenix WinNonlin 8. A mixed model with subject as random effect and day as fixed effect (day treated as a continuous variable) was performed by dose on the log_e-transformed predose concentration and Ctrough. Achievement of plasma GSK3640254 steady state was assessed by the point estimate and 90% CI of the slope of the day by dose group. Dose proportionality of single and multiple doses of GSK3640254 was assessed using a power model and analysis of variance. SAS® version 9.3 (SAS Institute, Cary, NC) or higher was used to analyze data descriptively.

For the relative bioavailability study, no formal sample size calculation was made. However, 14 participants were enrolled to achieve a minimum of 12 evaluable participants. Descriptive statistics were calculated by treatment for all PK concentrations over time and derived PK parameters. Log-transformed $AUC_{0-\infty}$ or AUC_{0-t} and Cmax values for GSK3640254 were subjected to mixed effects modeling, including terms for period and treatment as fixed effects and participant as random effect. The point estimate and associated 90% CI was constructed for the difference, mesylate salt formulation – bis-hydrochloride salt formulation. The point estimate and associated 90% CI were then back-transformed to provide a point estimate and 90% CI for the ratio mesylate salt formulation/bis-hydrochloride salt formulation on the original scale. Safety endpoints were summarized descriptively, and no formal statistical analysis was conducted.

3 | RESULTS

3.1 | Participant disposition and demographics

3.1.1 | Single and multiple ascending dose FTIH study

Seventy-eight participants, all men with a mean age across cohorts ranging from 34.1 to 42.2 years and mean BMI ranging from 23.6 to 27.6 kg/m^2, were included (Table 1). In Part 1, there were originally eight participants randomized in cohort 1 and eight participants randomized in cohort 2. In cohort 1, there were four participants who withdrew during the study before completion of period 4 (three because of AEs not related to study drug [viral infection, n = 2; depression, n = 1] and one for personal reasons). Upon withdrawal, a replacement participant was randomized to complete the remainder of the periods. Thus, at the completion of Part 1, 20 participants were ultimately randomized, 12 participants in cohort 1 and eight participants in cohort 2.

In Part 2, there were originally eight participants randomized to cohorts 3 to 6, and 24 participants randomized to the expansion cohort. In cohort 6, one participant randomized to GSK3640254 320 mg withdrew before study completion for personal reasons and was replaced. In the expansion cohort, one participant withdrew before study completion because of an AE of maculopapular rash and was replaced. Thus, at the completion of Part 2, 58 participants were ultimately randomized.

3.1.2 | Relative bioavailability study

This study randomized 14 healthy male participants, with a mean age of 33.9 years and mean BMI of 25.4 kg/m^2. Participants received single doses of 200 mg as the mesylate salt or the bis-hydrochloride salt formulation in each dosing period. All 14 participants were dosed and completed the study.

3.2 | Safety

3.2.1 | Single and multiple ascending dose FTIH study

GSK3640254, in single and multiple ascending doses, was generally well tolerated, and no deaths or serious AEs were reported. Across all drug doses in the 20 participants in Part 1, the most common AEs were headache (eight events), contact dermatitis (five events), diarrhea (four events), dizziness (four events), and nasopharyngitis (three events; Table 2). Because of the crossover nature of this trial, some participants reported the same AE with different doses. In Part 2, across 58 participants, the most common AEs were headache (25.9%), contact dermatitis (13.8%), and dizziness (12.1%; Table 2). Across both parts of the study, there were 12 adverse drug reactions (four events in two participants during single-dose administration and eight events in seven participants during multiple-dose administration; Table 3). All adverse drug reactions were mild except for one event of headache that was of moderate intensity in Part 2 (50-mg group). One participant in the 50-mg cohort had progressive increases in ALT during treatment with a peak ALT of 83 IU/L on Day 16 (baseline ALT was 49 IU/L) that was considered an adverse drug reaction. The remaining liver chemistry results were normal throughout and the participant remained on study treatment. One participant (2%) from the expansion cohort discontinued because of a grade 1 maculopapular rash, which was also considered an adverse drug reaction. The rash was mild in intensity and resolved with fexofenadine and topical steroids in 6 days.

Eleven GI AEs were reported in six (30%) participants in Part 1. Three AEs (two events of diarrhea and one event of abdominal pain) reported by one participant were considered adverse drug reactions. Eighteen GI AEs were reported in 13 (22%) participants in Part 2. Two events of nausea (one in the 200-mg + expansion cohort and one in the 320-mg cohort) were considered adverse drug reactions. All GI AEs were mild and resolved without intervention. No cardiac AEs, clinically significant arrhythmias, or QTcF prolongations (QTcF ≥ 500 msec or change from QTcF ≥ 60 msec) were observed in Part 1. One participant (2%) in Part 2 (200-mg + expansion cohort) reported an AE of isolated and limited palpitations (without any changes on ECG) that was mild in intensity and determined to be unrelated to study drug. There were no clinically significant trends in laboratory values or vital sign parameters across doses in either part of the single and multiple ascending dose study.

3.2.2 | Relative bioavailability study

In this study, six (43%) and three (21%) participants reported AEs after dosing with the mesylate salt and bis-hydrochloride salt formulations, respectively (Table 2). Of the 14 total participants, seven (50%) reported at least one AE, all of which were mild in intensity. Adverse events occurring in >1 participant were headache and pain in extremity (n = 2 each). One participant reported two adverse drug reactions of headache occurring after each regimen. No clinically significant changes in laboratory values, vital signs, or ECG parameters were observed.

3.3 | Pharmacokinetics

3.3.1 | Single and multiple ascending dose FTIH study

Absorption of GSK3640254 was slow, with median tmax occurring between 3.0 and 4.5 hours after administration; mean half-life was ~24 hours (21.2-25.3 hours) for the 10- to 700-mg doses.

TABLE 2 Adverse events reported in >1 participant associated with single- and multiple-dose administration of GSK3640254

	Single ascending dose part								
Event, n (%)	1 mg (N = 6)	3 mg (N = 6)	10 mg (N = 6)	30 mg (N = 6)	100 mg (N = 6)	200 mg (N = 6)	400 mg (N = 6)	700 mg (N = 6)	Placebo (N = 16)
Any event	3 (50)	2 (33)	4 (67)	3 (50)	3 (50)	4 (67)	4 (67)	1 (17)	7 (44)
Headache	1 (17)	0	1 (17)	1 (17)	2 (33)	1 (17)	2 (33)	0	1 (6)
Contact dermatitis	1 (17)	1 (17)	1 (17)	0	0	1 (17)	1 (17)	0	0
Diarrhea	0	0	1 (17)	1 (17)	2 (33)	0	0	0	1 (6)
Dizziness	1 (17)	1 (17)	1 (17)	0	0	0	0	1 (17)	0
Nasopharyngitis	0	0	1 (17)	0	1 (17)	0	1 (17)	0	0
Vomiting	0	0	0	0	2 (33)	0	0	0	0
Viral infection	0	0	1 (17)	0	1 (17)	0	0	0	0
Cough	0	0	1 (17)	0	1 (17)	0	0	0	0
Nasal obstruction	0	0	1 (17)	0	0	0	0	0	2 (13)
Nightmare	0	1 (17)	0	0	0	0	0	0	1 (6)
Increased transaminases	0	0	0	0	0	1 (17)	0	0	1 (6)
Gastrointestinal disorders	1 (17)	0	1 (17)	1 (17)	2 (33)	0	1 (17)	0	2 (13)

	Multiple ascending dose part				
Event, n (%)	50 mg (N = 6)	100 mg (N = 6)	200 mg[†] (N = 25)	320 mg (N = 7)	Placebo (N = 14)
Any event	4 (67)	5 (83)	19 (76)	6 (86)	10 (71)
Headache	3 (50)	1 (17)	3 (12)	2 (29)	6 (43)
Contact dermatitis	1 (17)	0	7 (28)	0	0
Dizziness	1 (17)	2 (33)	2 (8)	1 (14)	1 (7)
Contusion	1 (17)	1 (17)	3 (12)	0	1 (7)
Fatigue	2 (33)	1 (17)	1 (4)	0	2 (14)
Back pain	0	1 (17)	2 (8)	0	2 (14)
Catheter-site bruise	0	1 (17)	1 (4)	0	1 (7)
Lethargy	0	0	1 (4)	1 (14)	1 (7)
Abdominal distension	0	0	1 (4)	0	1 (7)
Abdominal pain	1 (17)	0	1 (4)	0	0
Abnormal dreams	0	0	2 (8)	0	0
Agitation	0	1 (17)	1 (4)	0	0
Arthropod bite	0	0	0	2 (29)	0
Catheter-site pain	0	0	0	1 (14)	1 (7)
Constipation	0	0	2 (8)	0	0
Disturbance in attention	0	0	1 (4)	0	1 (7)
Dry skin	0	0	0	1 (14)	1 (7)
Musculoskeletal stiffness	1 (17)	0	1 (4)	0	0
Nausea	0	0	1 (4)	1 (14)	0
Oropharyngeal pain	0	0	1 (4)	1 (14)	0
Rash	0	0	1 (4)	0	1 (7)
Somnolence	1 (17)	0	0	1 (14)	0
Vessel puncture site bruise	0	0	1 (4)	0	1 (7)
Gastrointestinal disorders	2 (33)	0	6 (24)	2 (29)	3 (21)

(Continues)

TABLE 2 (Continued)

Bioavailability study		
Event, n (%)	**Mesylate salt formulation (N = 14)**	**Bis-hydrochloride salt formulation (N = 14)**
Any event	6 (43)	3 (21)
Headache	2 (14)	1 (7)
Pain in extremity	2 (14)	0

†Includes participants from cohort 5 and the expansion cohort.

TABLE 3 Overview of adverse events in the single and multiple ascending dose study

	Single ascending dose part			Multiple ascending dose part				
Event, n	**Cohort 1 (N = 12)**	**Cohort 2 (N = 8)**	**Placebo (N = 16)**	**Cohort 3 50 mg (N = 6)**	**Cohort 4 100 mg (N = 6)**	**Cohort 5 200 mg† (N = 25)**	**Cohort 6 320 mg (N = 7)**	**Placebo (N = 14)**
AEs leading to discontinuation	3	0	0	0	0	1	0	0
Adverse drug reactions	1	2	1	3	0	2	2	1
All-cause AEs								
Grade 1 AEs	12	10	7	3	5	18	5	9
Grade 2 AEs	2	0	0	1	0	1	1	1
Grade 3/4 AEs	0	0	0	0	0	0	0	0

Cohort 1: 1-, 10-, 100-, and 400-mg single doses. Cohort 2: 3-, 30-, 200-, and 700-mg single doses.

Abbreviation: AE, adverse event.

†Includes participants from cohort 5 and the expansion cohort.

Dose-proportionality analysis of Cmax and AUC showed an approximately dose-proportional increase in exposure to GSK3640254 over the 1- to 700-mg dose range, with a slightly less than dose-proportional increase at higher doses and no increase in exposure from 400 to 700 mg (Figure 2; Table 4). After single-dose administration, GSK3640254 was detectable in plasma for up to 48 hours (1 and 3 mg) and up to 96 hours (10-700 mg; Figure 2).

Dose-proportionality analysis of Cmax and AUC after multiple-dose administration (50-320 mg) showed a trend toward less than dose-proportional increases in exposure with increasing dose (Figure 3). A comparison of GSK3640254 levels in plasma on Day 14 of multiple-dose administration showed 1.9- to 2.6-fold accumulation compared with Day 1. Statistical assessment of the attainment of steady state was performed on the trough concentrations from all participants. By Day 8, slope of trough concentration vs time data (Figure 4) was close to zero with the 90% CI of the slope containing zero.

3.3.2 | Relative bioavailability study

After single oral administration of a 200-mg dose of GSK3640254, the PK parameters of the mesylate salt were similar to those of the bis-hydrochloride salt, with Cmax values of 0.85 and 0.74 μg/mL, respectively, with tmax occurring at a median of 5 hours postdose and mean plasma half-life of ~24 hours (Figure 5). AUC from predose to 72 hours, the end of the PK collection ($AUC_{0\text{-}72}$), and Cmax of the mesylate salt were ~12% and ~16% higher, respectively, than those of the bis-hydrochloride salt (point estimate [90% CI] for mesylate salt/bis-hydrochloride salt formulation: $AUC_{0\text{-}72}$, 1.12 [0.99, 1.27]; Cmax, 1.16 [0.99, 1.35]). The upper limit of the 90% CI was outside 1.25; however, since this study was not designed as a powered study to assess formal equivalence between the two formulations, these differences were not considered clinically significant (ie, the PK for the two salt formulations were sufficiently similar and suitable for further evaluation in a phase IIa study).

4 | DISCUSSION

Viral maturation is a critical late-stage step in the HIV-1 life cycle that continues to remain a viable target for intervention.[1] We evaluated the safety and bioavailability of a next-generation MI, GSK3640254, in two phase I clinical trials. Like the previous structurally similar MI GSK3532795, GSK3640254 was well-tolerated and displayed a PK profile supportive of once-daily dosing with a range of doses that are anticipated to have antiretroviral activity. Furthermore, GSK3640254 did not show any clinically significant

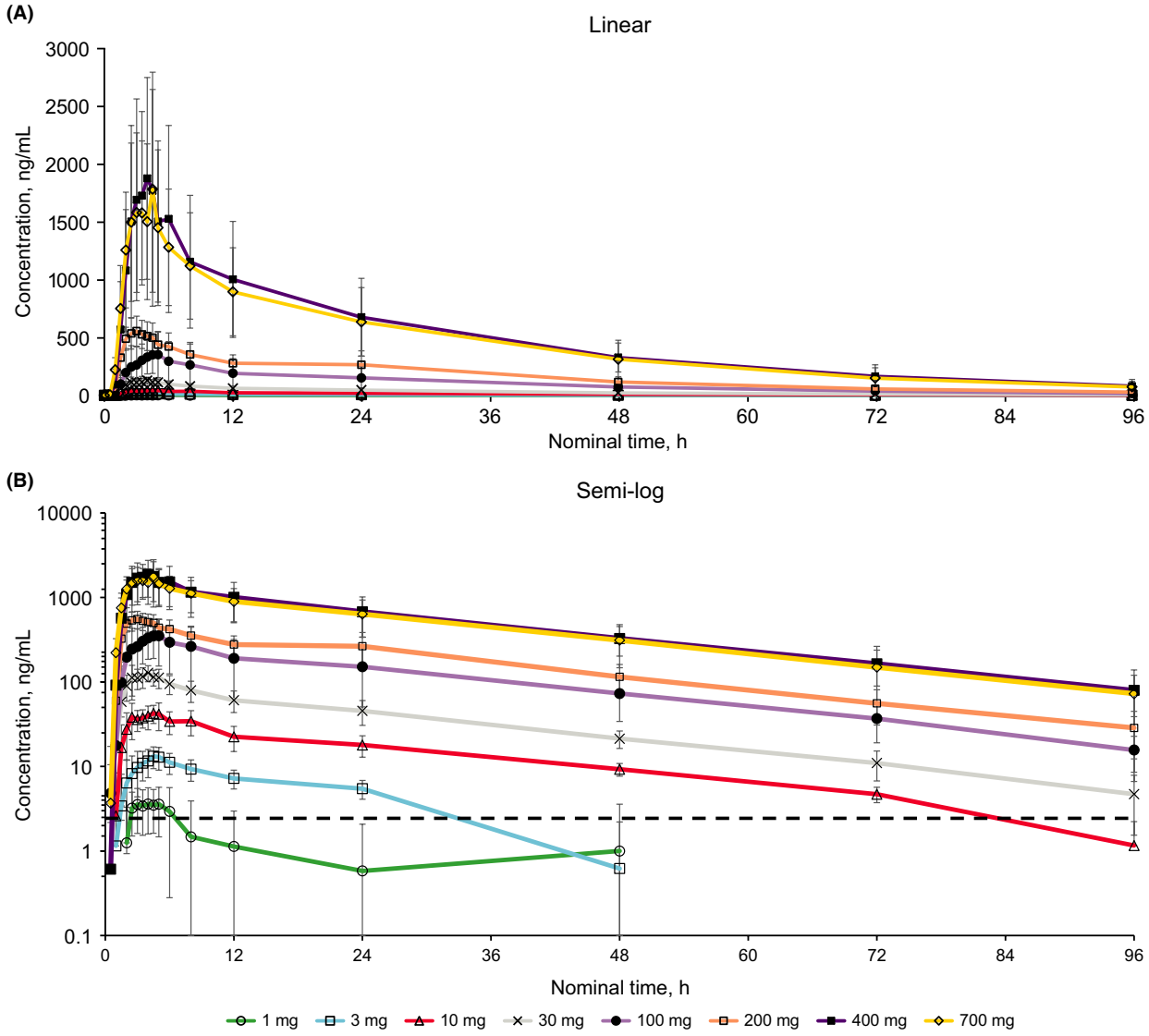

FIGURE 2 Mean (95% CI) plasma concentration of GSK3640254 in linear and semi-log scale in the single-dose part of the ascending dose study. The horizontal dashed line represents the lower limit of detection for the assay

adverse tolerability findings or trends through a maximum of 14 days of dosing. The relative bioavailability of the mesylate salt formulation was sufficiently similar to that of the bis-hydrochloride salt formulation used in the FTIH study to enable further evaluation in subsequent studies; the mesylate salt is an active pharmaceutical ingredient version that is preferred for development and commercial manufacture and has been used in other phase I/IIa clinical trials with GSK3640254. These results guided the choice of dose (ranges) that will be used for further development of GSK3640254 in other clinical trials.

Administration of GSK3640254 to healthy participants did not show any clinically significant adverse tolerability findings or trends through a maximum of 14 days of dosing. The most commonly reported AE between trials was headache. Few AEs were considered adverse drug reactions by the investigators and those were mild in severity except for one event of moderate headache in Part 2 of the ascending dose study. After single-dose administration in the ascending dose study, a plateau was observed where no difference was observed in AUC/Cmax upon increasing the dose from 400 to 700 mg. GSK3640254 was slowly absorbed after a moderate-calorie and -fat breakfast upon single- and multiple-dose administration with an estimated half-life of 21.2 to 28.4 hours, supporting once-daily dosing. Upon multiple-dose administration, there was a trend toward less than dose-proportional increase with increasing doses. Average Ctrough after daily multiple-dose administration of 50 to 320 mg ranged from 0.186 to 0.980 μg/mL. There was an approximately two- to three-fold increase in exposure upon repeat dosing, and steady state was reached within 8 days, both in agreement with the 24-hour half-life. In all, these data suggest that adequate drug exposure would be achieved with once-daily administration of GSK3640254.

In the single and multiple ascending dose study, GSK3640254 was administered as a bis-hydrochloride salt in an immediate-release capsule formulation. As the bis-hydrochloride salt formulation is susceptible to humidity, a more stable mesylate salt

TABLE 4 Pharmacokinetic data for single and multiple ascending dose administration of GSK3640254

Parameter, geometric mean (%CVb)[†]	N	Cmax, μg/mL	tmax, median (range), h	$AUC_{0-\infty}$, μg*h/mL	$t_{1/2}$, h
Single-dose administration					
1 mg	6	0.005 (16.4)	3.5 (2.5-6.0)	0.057 (39.4)	7.89[‡] (34.5)
3 mg	6	0.014 (31.0)	4.5 (2.0-5.0)	0.329 (34.3)	20.5 (21.1)
10 mg	6	0.047 (30.3)	3.5 (2.5-5.0)	1.23 (18.9)	25.3 (19.2)
30 mg	6	0.130 (21.1)	4.0 (2.5-5.0)	2.99 (26.3)	21.2 (18.2)
100 mg	6	0.372 (71.5)	3.8 (2.0-5.0)	8.54 (66.9)	22.8 (11.4)
200 mg	6	0.579 (27.0)	3.0 (2.0-4.0)	15.0 (41.1)	22.6 (21.7)
400 mg	6	1.88 (49.6)	3.3 (2.0-6.0)	43.0 (50.6)	23.7 (17.7)
700 mg	6	1.72 (41.3)	3.3 (2.0-4.5)	39.7 (50.4)	20.8 (24.2)
Multiple-dose administration, Day 1					
	N	Cmax, μg/mL	tmax, median (range), h	AUC_{0-24}, μg*h/mL	$t_{1/2(z)}$, h
50 mg	6	0.215 (24.4)	3.8 (3.0-5.0)	2.86 (29.6)	ND
100 mg	6	0.536 (23.0)	4.3 (2.0-5.0)	6.80 (23.0)	ND
200 mg[§]	25	0.614 (44.4)	4.0 (1.5-5.6)	8.26 (49.8)	ND
320 mg	7	1.04 (29.2)	4.0 (2.5-6.0)	13.5 (23.7)	ND
Multiple-dose administration, Day 14					
	N	Cmax, μg/mL	tmax, median (range), h	$AUC_{0-\tau}$, μg*h/mL	$t_{1/2(z)}$, h
50 mg	6	0.414 (31.6)	3.8 (2.5-5.0)	6.28 (34.0)	24.8 (5.1)
100 mg	6	1.18 (10.3)	4.0 (1.5-4.5)	17.5 (13.8)	28.4 (19.2)
200 mg[§]	24	1.40 (30.8)	3.8 (1.5-5.5)	21.5 (34.2)	22.1 (14.5)
320 mg	7	2.16 (20.4)	4.3 (1.5-6.0)	32.0 (35.4)	22.4 (12.6)
Relative bioavailability study					
	N	Cmax, μg/mL	tmax, median (range), h	$AUC_{0-\infty}$, μg*h/mL	$t_{1/2}$, h
Bis-hydrochloride salt formulation	14	0.74 (35.7)	5.0 (2.0-6.0)	23.6 (27.2)	24.1 (15.2)
Mesylate salt formulation	14	0.85 (40.5)	5.0 (2.0-6.0)	27.6 (46.7)	24.1 (15.9)

Abbreviations: AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours; $AUC_{0-\infty}$, AUC from time zero extrapolated to infinity; $AUC_{0-\tau}$, AUC from predose to the end of the dosing interval at steady state; Cmax, maximum concentration; CVb, between-participant coefficient of variation; ND, not defined; tmax, time to Cmax; $t_{1/2}$, terminal half-life; $t_{1/2(z)}$, elimination half-life.

[†]Unless otherwise noted.

[‡]Terminal phase not optimally defined because of sample concentrations falling below lower limit of quantitation.

[§]Includes participants from cohort 5 and the expansion cohort.

formulation was explored for later-phase studies and, potentially, commercial use.[6] Systemic exposure was sufficiently similar between the mesylate salt and bis-hydrochloride salt formulations, with a median tmax of 5 hours. Peak and overall exposure were similar between the formulations, although there was a 12% and 16% increase in AUC_{0-72} and Cmax, respectively, with the mesylate salt formulation, which was not considered clinically significant (no formal statistical testing was performed). GSK3640254 was administered after a moderate-fat meal, to address some of the bioavailability and dose-proportionality concerns that were observed with a previous MI in development, GSK3532795. It is possible that this might have limited our ability to detect any differences between the two salt formulations.

Although these studies provide the first evidence of safety and PK with this next-generation MI, there are some limitations. Sample sizes were small and only men were enrolled, even though women of nonchildbearing potential were eligible; hence, the results may not be generalizable to the global population with

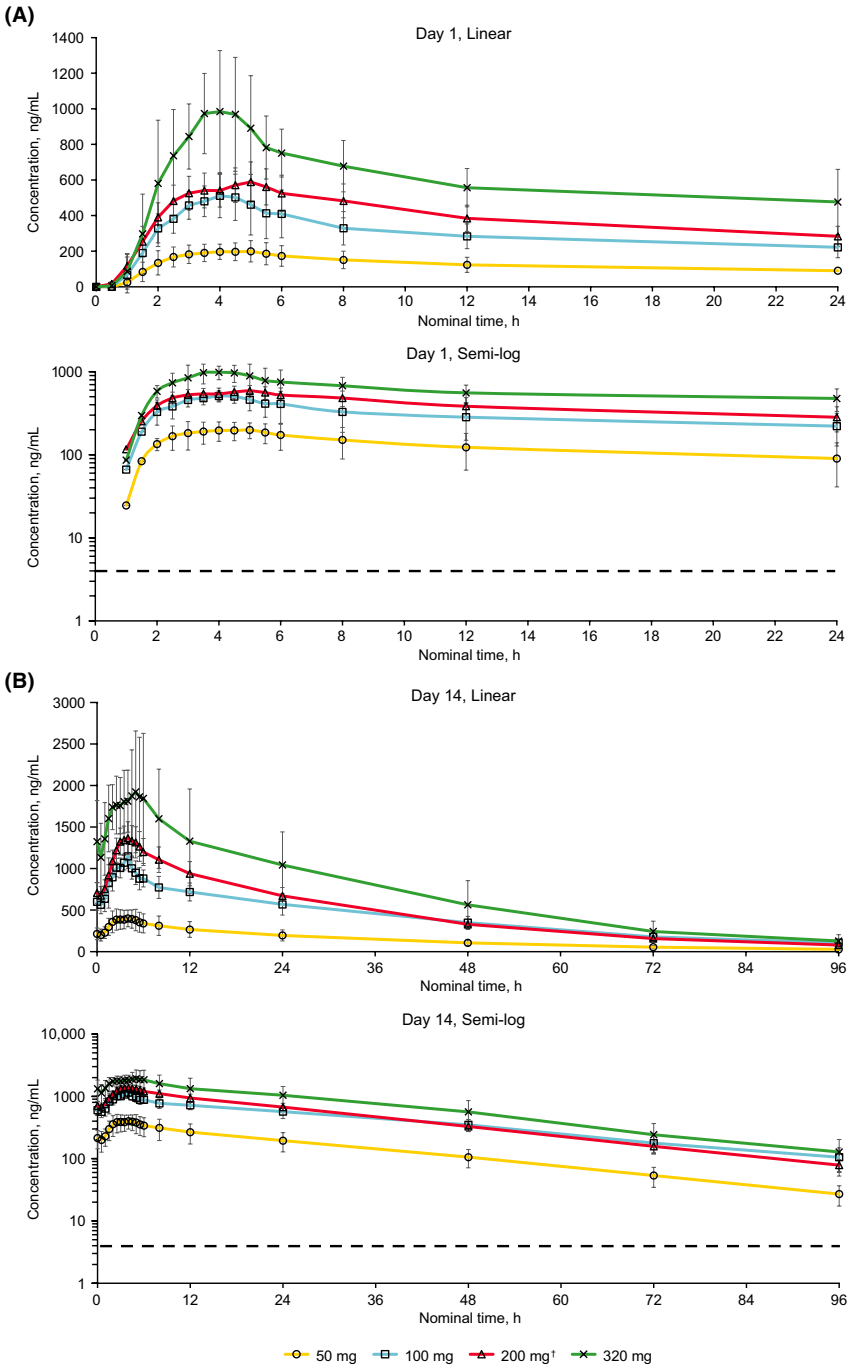

FIGURE 3 Mean (95% CI) plasma concentration of GSK3640254 in linear and semi-log scale in the multiple-dose part of the ascending dose study (Days 1 and 14). The horizontal dashed line represents the lower limit of detection for the assay. †Includes participants from cohort 5 and the expansion cohort

HIV-1. However, based on the results from a previous MI study in which women were enrolled,[7] we do not anticipate differences in PK properties due to gender. Women of childbearing potential were not eligible for study participation because the effect of GSK3640254 on fetal development was unknown during the conduct of the trial.

In conclusion, single and multiple doses of GSK3640254 were not associated with major tolerability findings, and the PK profiles of the mesylate salt formulation and the bis-hydrochloride salt formulation demonstrated generally similar bioavailability. Based on the safety and PK profiles observed in the two studies described here, a range of doses will be evaluated in a phase IIa proof-of-concept study in HIV-1–infected, treatment-naive individuals (Study 208132, NCT03784079).

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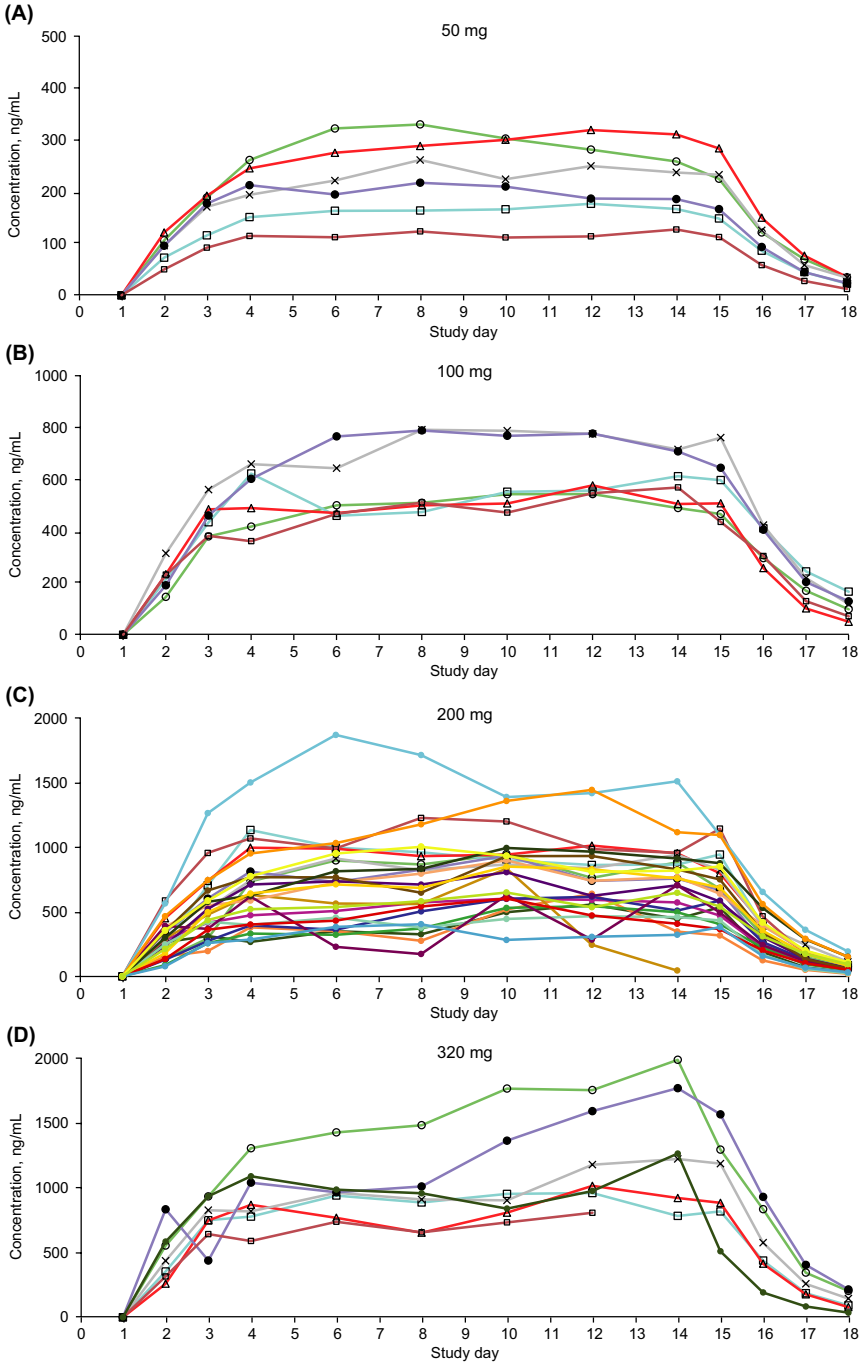

FIGURE 4 Plasma GSK3640254 predose daily concentration troughs over time for all participants in Part 2 in the (A) 50-mg, (B) 100-mg, (C) 200-mg, and (D) 320-mg cohorts. [a]Predose (trough) concentrations shown for Days 1-14; last dose was taken on Day 14. Days 15-18 are follow-up visits. [b]Lower limit of quantification equals 3 ng/mL

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DISCLOSURES

Samit R. Joshi, Max Lataillade, and Sherene Min are employees of ViiV Healthcare; Max Lataillade and Sherene Min own stock in GlaxoSmithKline (GSK). Disala Fernando, Stephanie Igwe, Anu S. Krishnatry, Fiona Halliday, Joyce Zhan, Thomas J. Greene, Jianfeng Xu, and Geraldine Ferron-Brady are employees of GSK and own stock in GSK. Litza McKenzie is an employee of Quotient Sciences, which was contracted by GSK to perform the clinical aspects of the relative bioavailability study, and she served as the principal investigator; Dr McKenzie receives a fixed wage from Quotient Sciences, which is not dependent on the conduct or outcome of any individual study.

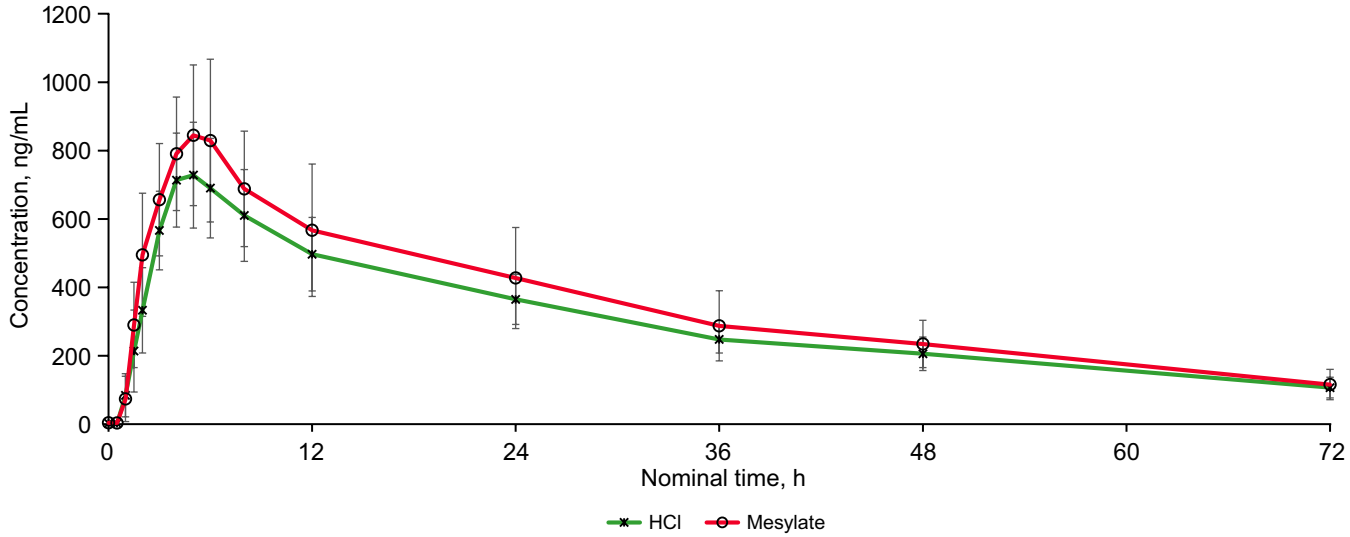

FIGURE 5 Mean (95% CI) plasma concentration of GSK3640254 in linear scale in the relative bioavailability study

AUTHOR CONTRIBUTIONS

Samit R. Joshi, Disala Fernando, Stephanie Igwe, Litza McKenzie, Anu S. Krishnatry, Fiona Halliday, Joyce Zhan, Thomas J. Greene, Jianfeng Xu, Geraldine Ferron-Brady, Max Lataillade, and Sherene Min contributed to the conception of the studies; the design of the studies; the acquisition, analysis, and interpretation of data; drafting of the manuscript; critically revising the manuscript for important intellectual content; and approval of the manuscript for publication.

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.

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