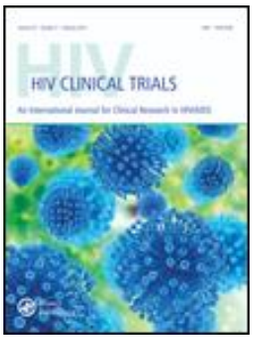

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Pharmacokinetics, Safety, and Monotherapy Antiviral Activity of GSK1265744, an HIV Integrase Strand Transfer Inhibitor

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Background: GSK1265744 is an HIV integrase strand transfer inhibitor selected for clinical development. **Objective:** This first-time-in-human and phase IIa investigation assessed GSK1265744 antiviral activity, pharmacokinetics, safety, and tolerability in healthy and HIV-1–infected subjects. **Methods:** This double-blind, placebo-controlled study consisted of a dose escalation of single (part A) and multiple (part B) oral doses in 48 healthy subjects and an oral dose (part C) in 11 HIV-1–infected subjects. In part A, 2 cohorts of 9 subjects received either 5 and 25 mg or 10 and 50 mg. In part B, 3 cohorts of 10 subjects received 5, 10, or 25 mg once daily for 14 days. In part C and the phase IIa study, subjects received 5 or 30 mg once daily for 10 days. **Results:** Dose-proportional increases in drug exposure were observed in healthy and HIV-1–infected subjects. In healthy subjects, pharmacokinetic variability was low following single or repeat dosing (coefficient of variation, 13%-34% and 15%-23%, respectively). Mean plasma half-life was 31.5 hours. GSK1265744 monotherapy significantly reduced plasma HIV-1 RNA from baseline to day 11 in HIV-1–infected subjects receiving 5 or 30 mg versus placebo ($P < .001$); mean decrease was 2.2 to 2.3 $\log_{10}$ copies/mL, respectively. Study drug was generally well tolerated with no clinically relevant trends in laboratory values, vital signs, or electrocardiograms. **Conclusions:** GSK1265744 was well tolerated in healthy and HIV-1–infected subjects. Results demonstrate once-daily doses of 5 or 30 mg exceeded minimum target therapeutic concentrations and produced a significant reduction in plasma HIV-1 RNA viral load. **Key words:** *antiretroviral agent, dose-response relationship, GSK1265744, HIV-1, HIV integrase inhibitor, pharmacokinetics*

Combination therapy with highly active antiretroviral therapy (ART) has significantly improved AIDS-related morbidity and mortality, extending the expected lifespan of patients with HIV.[1] In addition, the availability of newer classes of antiretroviral agents, such as the chemokine receptor 5 antagonists and integrase strand transfer inhibitors (INSTIs), has expanded treatment and regimen sequencing options. The US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents now recommends the INSTIs raltegravir (RAL) and elvitegravir (EVG) as preferred and alternative agents, respectively, for use in the treatment of ART-naïve patients.[2] However, treatment-emergent resistance has been observed in patients failing regimens containing these agents,[3,4] and cross-resistance between RAL and EVG has been reported.[5] Additional factors such as twice-daily dosing (RAL) or required pharmacokinetic (PK) enhancement (EVG) via coadministration with cytochrome (CYP) P450 3A isozyme inhibitors such as ritonavir or cobicistat offer a rationale to pursue improved INSTI drugs.

GSK1265744 is an INSTI from the carbamoyl pyridone class of compounds and an analogue

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of the INSTI dolutegravir. Studies with human liver microsomes and recombinant enzymes indicate involvement of uridine diphosphate glucuronyltransferase (UGT) in the metabolism of GSK1265744, but the fractional clearance by UGT and possible CYP P450 enzyme involvement in humans have not yet been fully characterized (ViiV Healthcare, unpublished data). GSK1265744 was selected for clinical development based on (1) the potential for a high genetic barrier to resistance demonstrated through in vitro testing and (2) a PK profile allowing low-dose once-daily oral dosing or monthly to quarterly parenteral dosing using a nanosuspension formulation suitable for intramuscular or subcutaneous injection.[6-9] Long-acting injectable antiretroviral drugs have been proposed as pre-exposure prophylaxis (PrEP) agents and have shown the potential for high acceptance in a survey among potential user groups.[10] The first-time-in-human (FTIH) studies were undertaken to assess the PK, safety, and tolerability of orally administered GSK1265744 in healthy and HIV-1–infected subjects and to evaluate the antiviral activity of short-term monotherapy with GSK1265744 versus placebo in adults with HIV-1 infection.

METHODS

Subjects

Adult subjects (≥18 and ≤65 years of age) who did not have a pre-existing condition potentially interfering with the absorption, metabolism, or excretion of the study drug and who had not recently received another investigational product were eligible for enrollment. Female subjects were required to be of nonchildbearing potential (postmenopausal or premenopausal with a documented bilateral tubal ligation, bilateral oophorectomy, or hysterectomy). Subjects were not eligible if they had positive results at screening for hepatitis B surface antigen, hepatitis C (HCV) antibody, or detectable HCV RNA. Subjects infected with HIV-1 were eligible for part C of the FTIH study and for the phase IIa study if they had a CD4+ cell count ≥200 cells/mm^3 and a plasma HIV-1 RNA concentration ≥5000 copies/mL, had not received any ART in the 12 weeks before the first study dose, and had adequate treatment options to construct highly active ART with at least 3 active ARTs for future treatment. Any HIV-infected subjects with an active Centers for Disease Control and Prevention (CDC) category C disease (except cutaneous Kaposi's sarcoma not requiring systemic therapy during the trial) were excluded.

Clinical Protocol

Each of the studies was conducted in accordance with good clinical practice procedures, all applicable regulatory requirements, and the guiding principles of the Declaration of Helsinki. Studies were approved by an ethics committee or institutional review board. All subjects provided written informed consent before study entry.

First-time-in-human PK study

This double-blind, randomized, placebo-controlled study (NCT00659191) consisted of 3 parts: an oral dose-escalation study of a single dose (part A) and multiple doses (part B) in healthy subjects and a multiple oral dose study (part C) in HIV-1–infected subjects. GSK1265744 dose selection was based on the no observed adverse effect level exposures in preclinical toxicity studies and in consideration of predicted human PK and the target antiviral concentration (protein binding–adjusted 90% inhibitory concentration [PA-IC$_{90}$] value of 166 ng/mL).[11] Dose adjustment was permitted during the course of the study as PK and safety results were reviewed and used to predict subsequent exposure targets. The GlaxoSmithKline study team was unblinded in order to assess safety and PK data on a real-time basis while making dose-escalation decisions. All doses were administered orally in the morning following an overnight fast of at least 10 hours. In part A, 2 cohorts of 9 healthy subjects were randomized to single oral suspension doses in either 5 and 25 mg or 10 and 50 mg of GSK1265744 or placebo (in a 7:2 ratio) in 2 separate visits (**Table 1**). During repeat-dose part B, 3 cohorts of 10 healthy subjects each were randomized to oral suspension doses of 5, 10, or 25 mg or placebo once daily for 14 days. On the basis of the preliminary single and repeat PK data from part A and part B, study part C was undertaken and 10 HIV-1–infected subjects were randomized to 30 mg (six 5-mg tablets) or placebo for 10 days to explore the maximum antiviral activities (**Table 1**). Part C was included in the study because of the high plasma protein binding of GSK1265744 (free

Table 1. Study design and enrollment allocation

Study design	Part	Sample size	Period 1	Period 2
Phase I: FTIH	Part A	Cohort 1 (n = 7)	5 mg	25 mg
		Cohort 2 (n = 7)	10 mg	50 mg
		Cohorts 1 & 2 placebo (n = 4)	Placebo	Placebo
	Part B	Cohort 1 (n = 8)	5 mg × 14 days, qd	
		Cohort 2 (n = 8)	10 mg × 14 days, qd	
		Cohort 3 (n = 8)	25 mg × 14 days, qd	
		Cohorts 1, 2, 3 placebo (n = 6)	Placebo × 14 days, qd	
	Part C	Cohort 1, (n = 8)	30 mg × 10 days, qd	
		Cohort 1 placebo (n = 2)	Placebo × 10 days, qd	
Phase IIa: POC		Cohort 1 (n = 8)	5 mg × 10 days, qd	
		Cohort 1 placebo (n = 2)	Placebo × 10 days, qd	

Note: FTIH = first time in human; POC = proof of concept; qd = once daily.

fraction of <1%) and uncertainty of therapeutic target concentration; thus, a well-tolerated higher exposure from part B was selected for evaluation in HIV-1–infected subjects. To minimize the risk of selection and outgrowth of drug-resistant HIV-1 during the period when GSK1265744 plasma concentrations were waning and predicted to be nearing the PA-IC_{90} value, from day 14 onward, subjects were administered a minimum of 14 days of investigator-selected 3-drug ART. The treatment for part C was unblinded on day 11, allowing subjects receiving placebo the option to decline 3-drug ART. All subjects were followed for a minimum of 7 to 14 days after receiving the last dose of investigational drug.

Phase IIa study

The objective of this double-blind, randomized, placebo-controlled study (NCT00920426) was to evaluate lower GSK1265744 doses after obtaining the antiviral activities from the 30-mg dose used in the FTIH study. Ten HIV-1–infected subjects were randomized at a ratio of 8:2 to receive 10 days of GSK1265744 5 mg (one 5-mg tablet in the morning following an overnight fast of at least 6 hours) monotherapy or placebo followed by 14 days of investigator-selected 3-drug ART for the reasons stated previously, commencing on day 11. Treatment was unblinded on day 11 so that subjects receiving placebo had the option to decline 3-drug ART. All subjects were followed for a minimum of 14 days after the last dose of investigational drug. On the basis of the safety and antiviral activity observed in this group, the protocol permitted additional cohorts to be enrolled to evaluate a lower dose (1 mg) or higher dose (15 mg) of GSK1265744. However, on the basis of the observed antiviral activity, the study sponsor elected to end the study after completion of the 5-mg dose cohort.

Assessments

The primary endpoints of both studies included PK, change in plasma HIV-1 RNA from baseline to day 11, and safety and tolerability. Secondary endpoints for both studies included estimation of accumulation ratios, achievement of steady state, change from baseline in plasma HIV-1 RNA, and emergence of viral drug resistance. In the FTIH study, assessment of PK parameters at different doses was an additional secondary endpoint. In the phase IIa study, additional secondary endpoints included rate of decline of plasma HIV-1 RNA over 11 days, proportion of subjects with HIV-1 RNA <400 copies/mL, proportion of subjects with HIV-1 RNA <50 copies/mL, and change from baseline in CD4+ cell counts to day 11. Efficacy in both studies was analyzed in the intent-to-treat (ITT) population (ie, patients with ≥1 dose of study drug and with ≥1 postbaseline plasma HIV-1 RNA measurement). The safety population in both studies included patients who received ≥1 dose of study medication.

Serial blood PK samples were collected throughout each study, with full profiling for all subjects on days 1 and 10 (part C of FTIH and phase IIa study) and day 14 (part B FTIH only). Specific sampling

times in parts A and B on study days 1 and 14 were predose (within 15 minutes prior to dosing) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours postdose. In part C, plasma samples were collected on days 1 and 10 at predose (within 15 prior to dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours postdose. Single predose samples were taken in the morning on days 2, 3, 4, 7, 8, and 9; day 11 (24 hours following the final dose); and day 14 ± 1 (prior to starting optimized therapy). In the phase IIa study, serial plasma samples were collected on days 1 and 10 predose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours postdose. Single PK samples were collected within 15 minutes prior to dosing on days 2, 3, 4, 7, 8, 9, and 11 (24 hours following the final dose).

Plasma GSK1265744 concentrations were determined by Worldwide Bioanalysis (GlaxoSmithKline, Research Triangle Park, NC, USA) using a validated liquid chromatography–mass spectrometry method with a lower limit of quantification of 10 ng/mL. Additional PK parameters assessed included area under the plasma concentration-time curve (AUC), maximum observed plasma concentration (Cmax), minimum observed plasma concentration (Cmin), concentration at the end of the dosing interval (C_τ), time to maximum concentration (tmax), terminal elimination phase half-life ($t_{1/2}$), and apparent oral clearance.

HIV-1 RNA samples were collected from screening to follow-up. Screening and baseline HIV-1 RNA were assessed using a standard HIV-1 RNA polymerase chain reaction (PCR) assay (lower limit of detection [LLOD] of 400 copies/mL); postbaseline assessments used an ultrasensitive assay with an LLOD of 50 copies/mL. Whole venous blood samples were obtained from each subject for analysis of lymphocyte subsets and to provide plasma for resistance analyses carried out by Monogram Biosciences using their PhenoSense assays (Monogram Biosciences, Inc, South San Francisco, CA, USA). Safety parameters, including adverse events (AEs), laboratory tests (chemistry, hematology, and urinalysis), concomitant medications, vital signs, and electrocardiograms (ECGs) were evaluated intermittently throughout the studies. Adverse events and laboratory abnormalities were assessed using the National Institute of Allergy and Infectious Diseases, Division of Acquired Immunodeficiency Syndrome grading table.[12]

Statistical Analyses

The sample sizes for the studies were based primarily on feasibility to provide adequate precision for the estimates. Baseline characteristics, safety data, PK parameters, and viral genotypic/phenotypic data were summarized using descriptive statistics. Data from HIV-1–infected subjects from both studies were combined to examine dose proportionality of GSK1265744 (using the power model $y = \alpha \cdot dose^{\beta}$) and to assess PK/pharmacodynamic (PD) relationships using linear and maximum effect (Emax) models with SAS PROC NLMIXED (SAS version 9.1; SAS Institute Inc, Cary, NC, USA). Plasma HIV-1 RNA changes from baseline to day 11 were summarized by treatment and compared between each active treatment and placebo group using analysis of covariance.

RESULTS

The FTIH study was conducted from February 13, 2008 to November 18, 2008. Eighteen subjects were enrolled in the single-dose, dose-escalation phase in healthy adults (part A; **Table 2**). Of the 30 subjects enrolled in the repeat-dose, dose-escalation phase in healthy adults (part B), 3 cohorts of 8 subjects each received GSK1265744 in multiple doses of 5, 10, or 25 mg, and 6 subjects received placebo (**Table 2**). In the repeat-dose phase in HIV-1–infected subjects (part C), 11 subjects were randomized to receive GSK1265744 30 mg (n = 8) or placebo (n = 3). All subjects had CDC category A disease: asymptomatic lymphadenopathy or acute HIV-1 (**Table 2**). All 8 subjects randomized to GSK1265744 in part C received optimized therapy with multiple antiretroviral agents from day 14 onward. All subjects in the FTIH study were included in the safety population. All subjects in part C of the FTIH study were included in the ITT population.

The phase IIa proof-of-concept (POC) study was conducted from June 9, 2009 to August 13, 2009. A total of 9 subjects (7 in the GSK1265744 5-mg group and 2 in the placebo group) were enrolled. Demographic characteristics are provided in **Table 2**. Except for 1 subject in the placebo arm, all subjects began optimized therapy on day 11. All subjects were included in the safety and ITT populations.

Table 2. Overall demographics and baseline characteristics

	Phase I: FTIH			Phase IIa: POC	
Characteristic	Part A (n = 18)	Part B (n = 30)	Part C (n = 11)	GSK1265744 5 mg (n = 7)	Placebo (n = 2)
Male, n (%)	16 (89)	29 (97)	11 (100)	5 (71)	2 (100)
Race, n (%)					
Black	2 (11)	5 (17)	0	2 (29)	0
White	15 (83)	24 (80)	11 (100)	5 (71)	2 (100)
Other	1 (6)	1 (3)	0	0	0
Age, mean (SD), years	31.3 (11.3)	28.9 (9.1)	39.6 (8.8)	39.7 (5.8)	37.5 (9.2)
Weight, mean (SD), kg	77.7 (9.7)	76.9 (9.8)	84.3 (8.7)	83.2 (14.3)	89.9 (8.9)
Plasma HIV-1 RNA, mean (SD), log_{10} copies/mL	NA	NA	744: 4.140 (0.267) Placebo: 5.093 (0.425)	4.48 (0.49)	4.40 (0.82)[a]
CD4+ cell count, median (range), cells/mm^3	NA	NA	744: 395 (330-740) Placebo: 350 (320-450)	320.0 (163-415)	479.0 (461-497)
Prior antiretroviral therapy, n (%)	NA	NA	NR	4 (57)	1 (50)
CDC classification, n (%)	NA	NA			
A: Asymptomatic, lymphadenopathy, or acute HIV-1			744: 8 (100) Placebo: 3 (100)	7 (100)	2 (100)
B: Symptomatic, not AIDS				0	0
C: AIDS				0	0

Note: 744 = GSK1265744; CDC = Centers for Disease Control and Prevention; FTIH = first time in human; NA = not applicable; NR = not reported; POC = proof of concept; SD = standard deviation.

[a]Baseline HIV-1 RNA for 1 subject was lost, thus the subject's screening viral load HIV-1 RNA was used to calculate the "baseline" HIV-1 RNA.

Pharmacokinetics

Phase I FTIH study

Mean (standard deviation [SD]) plasma GSK1265744 concentration-time profiles following single dose and 14 days of repeat administration are shown in **Figure 1A** and **B.** GSK1265744 was readily absorbed; median tmax in healthy subjects was achieved between 0.5 and 1.5 hours across doses (**Table 3**). Intersubject variability in PK parameters was low to moderate following either single-dose administration (coefficient of variation [CV], 13%-34%) or 14 days of administration (CV, 15%-23%) of GSK1265744. There were dose-proportional increases in $AUC_{0-\tau}$, Cmax, C_τ, and Cmin over the 5- to 25-mg dose range with repeat-dose administration in healthy subjects (part B). Following repeat-dose administration in HIV-1–infected subjects (part C), geometric mean accumulation ratio for AUC was 2.51, similar to that observed following 14 days of repeat administration to healthy subjects (range, 2.38-2.52). Mean effective plasma $t_{1/2}$ was 31.5 hours, and day 10 geometric mean C_τ following 30 mg in HIV-1–infected subjects (3.28 µg/mL) exceeded the PA-IC_{90} by 20-fold. Steady state was achieved by approximately day 12 for all doses in healthy subjects (part B) and by day 7 following repeat administration of 30 mg in HIV-1–infected subjects (part C).

Phase IIa study

GSK1265744 was readily absorbed with no apparent lag time following both single- and repeat-dose administration, and Cmax was achieved 2 hours after dosing on day 1 and on day 10 (**Table 4**). Plasma concentrations of GSK1265744 reached steady state by day 7. Plasma steady-state C_τ for the 5-mg dose was approximately 3.5 times the in vitro PA-IC_{90} value of 0.166 µg/mL.[8] After 10 days

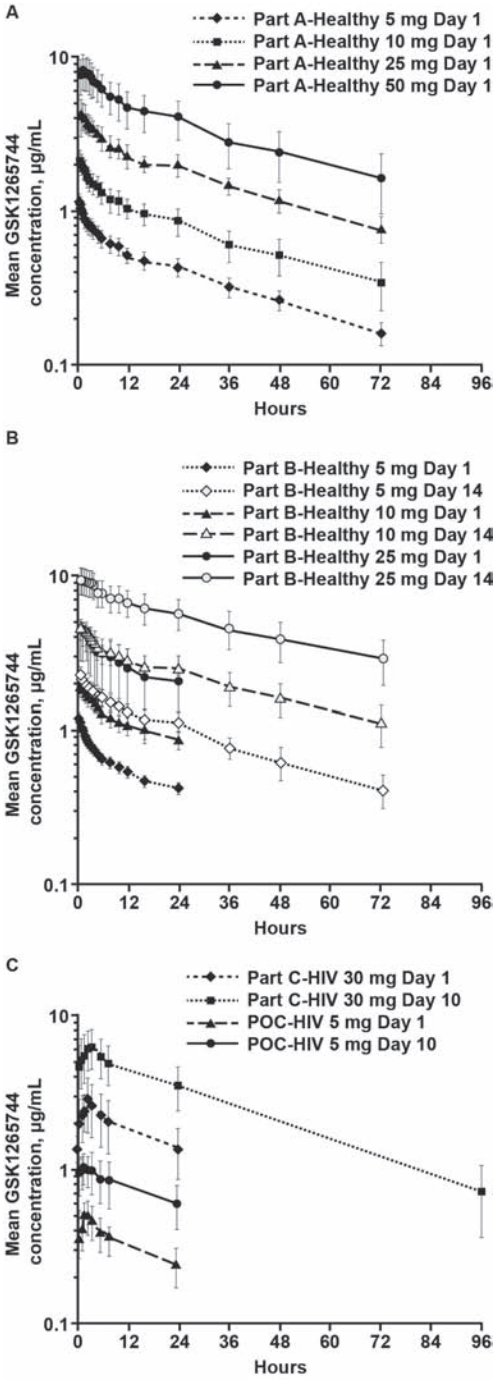

Figure 1. Mean (SD) plasma GSK1265744 concentration-time profiles following oral administration. (**A**) Single dose of 5, 10, 25, and 50 mg oral suspension to healthy study subjects. (**B**) Days 1 and 14 following administration of 5, 10, and 25 mg oral suspension to healthy study subjects. (**C**) Days 1 and 10 following administration of 5 and 30 mg oral tablets to HIV-infected study subjects. POC = proof-of-concept; SD = standard deviation.

of repeat-dose administration, the mean accumulation ratios for AUC, Cmax, and C_τ were estimated to be 2.36 (90% confidence interval [CI], 2.09-2.66), 1.96 (90% CI, 1.68-2.28), and 2.48 (90% CI, 2.14-2.88), respectively.

Data from subjects receiving GSK1265744 5 mg in the phase IIa study and from subjects receiving GSK1265744 30 mg from part C of FTIH were combined to allow assessment of dose proportionality and PD parameters. On the basis of an analysis of the combined data, the increase in GSK1265744 exposure (AUC, Cmax, C_τ) was dose proportional after both single- (day 1) and repeat-dose administration (day 10). Mean (SD) plasma GSK1265744 concentration-time profiles following first dose and 10 days of repeat administration in HIV-infected subjects are shown in **Figure 1C**. Given the observed, similar antiviral effects across the 2 doses studied, there were no significant correlations between GSK1265744 exposure and change in plasma HIV-1 RNA from baseline to day 11. A simple Emax model was fit to the day 11 HIV-1 viral load change from baseline versus C_τ data (**Figure 2**). The Emax was well estimated at 2.56 $\log_{10}$ (CV, 6%). The EC_{50}, estimated to be 0.082 µg/mL (CV, 69%), was limited by lack of data in the lower range of C_τ (observed range, 0.38-4.8 µg/mL). Lower doses would be required to fully evaluate the PK/PD relationship.

Antiviral Activity

HIV-1–infected subjects receiving GSK1265744 30 mg in the FTIH study had a statistically significant reduction in plasma HIV-1 RNA from baseline to day 11 compared with placebo ($P < .001$), with a mean change from baseline of -2.34 $\log_{10}$ copies/mL in the GSK1265744 30-mg group; subjects receiving GSK1265744 5 mg in the phase IIa POC study had a statistically significant reduction in plasma HIV-1 RNA from baseline to day 11 compared with placebo ($P < .001$), with a mean change from baseline of -2.17 $\log_{10}$ copies/mL in the GSK1265744 5-mg group versus -0.18 $\log_{10}$ copies/mL in the combined placebo group. Antiviral response was sustained through day 14 when 3-drug ART was initiated (**Figure 2**). A higher proportion of subjects receiving GSK1265744 30 mg had <50 copies/mL of plasma HIV-1 RNA on day 14 than those in the placebo group (75% vs 0%, respectively). A numeric increase in CD4+ cell counts also was

Table 3. Select plasma GSK1265744 pharmacokinetic parameters[a] following single-dose and repeat-dose administration with suspension formulation in healthy subjects

Single-dose administration study (part A)					
Treatment	n	Cmax (µg/mL)	tmax (h)[b]	AUC_{0-72} (µg·h/mL)	C_{24} (µg/mL)
5 mg	7	1.15 (16)	0.50 (0.50-1.00)	26.6 (14)	0.42 (13)
10 mg	7	2.15 (17)	1.00 (0.50-1.00)	51.7 (22)	0.83 (22)
25 mg	7	4.38 (23)	1.50 (0.50-3.00)	117 (13)	1.93 (16)
50 mg	7	8.57 (24)	1.50 (0.50-3.00)	231 (34)	3.82 (34)
Repeat-dose administration study, day 14 (part B)					
Treatment	n	Cmax (µg/mL)	tmax (h)	AUC_{0-24} (µg·h/mL)	Cmin (µg/mL)	C_{τ} (µg/mL)
5 mg	8	2.08 (19)	0.63 (0.25-1.50)	32.5 (16)	0.99 (21)	1.06 (20)
10 mg	8	4.29 (15)	0.88 (0.50-1.50)	69.2 (18)	2.04 (22)	2.39 (23)
25 mg	8	9.47 (19)	1.25 (0.50-4.00)	160 (20)	5.22 (22)	5.40 (22)

Note: AUC = area under the plasma concentration-time curve; C_{24} = concentration 24 hours after the first dose; C_{τ} = concentration at the end of the dosing interval; Cmax = maximum observed plasma concentration; Cmin = minimum observed plasma concentration; h = hours; tmax, time to maximum concentration.

[a]Unless otherwise specified, values are geometric mean (percent coefficient of variation).

[b]Values are median (range).

Table 4. Select plasma GSK1265744 pharmacokinetic parameters in part C of FTIH study and phase IIa study with tablet formulation in HIV-1–infected subjects

	Single-dose administration (day 1)		Repeat-dose administration (day 10)	
Parameters[a]	5 mg (n = 7)	30 mg (n = 8)	5 mg (n = 7)	30 mg (n = 8)
Cmax (µg/mL)	0.52 (20)	2.84 (32)	1.02 (25)	6.37 (23)
tmax (h)[b]	2.00 (1.00-4.00)	1.50 (1.00-3.00)	2.00 (1.50-4.08)	2.50 (1.00-4.00)
AUC_{0-24} (µg·h/mL)	7.53 (23)	41.5 (35)	—	104 (28)
$AUC_{0-\tau}$ (µg·h/mL)	—	—	17.7 (31)	—
C_{24} (µg/mL)	0.23 (28)	1.25 (39)	—	3.28 (36)
Cmin (µg/mL)	—	—	0.53 (35)	2.85 (35)
C_{τ} (µg/mL)	—	—	0.57 (33)	—

Note: AUC = area under the plasma concentration-time curve; C_{24} = concentration 24 hours after the first dose; C_{τ} = concentration at the end of the dosing interval; Cmax = maximum observed plasma concentration; Cmin = minimum observed plasma concentration; tmax = time to maximum concentration.

[a]Unless otherwise specified, values are geometric mean (percent coefficient of variation).

[b]Values are median (range).

observed in subjects receiving GSK1265744 30 mg (median change, +15 cells/mm^3), while CD4+ cell counts decreased in subjects who received placebo (median change, -90 cells/mm^3).

The plasma HIV-1 RNA rate of decline showed a statistically significant decrease for GSK1265744 5 mg compared with placebo in the phase IIa POC study (-0.2313 vs 0.0013, respectively) (**Figure 3**). In addition, the majority of subjects (71%) receiving GSK1265744 5 mg reached a plasma HIV-1 RNA concentration <400 copies/mL by day 11, while 2 subjects (29%) in this group reached a plasma HIV-1 RNA concentration <50 copies/mL by day 11. Numeric increases in CD4+ cell counts were observed on day 11 for subjects receiving GSK1265744 5 mg (mean change, 71 cells/mm^3). In contrast, CD4+ cell counts decreased in subjects who received placebo (mean change, -84 cells/mm^3).

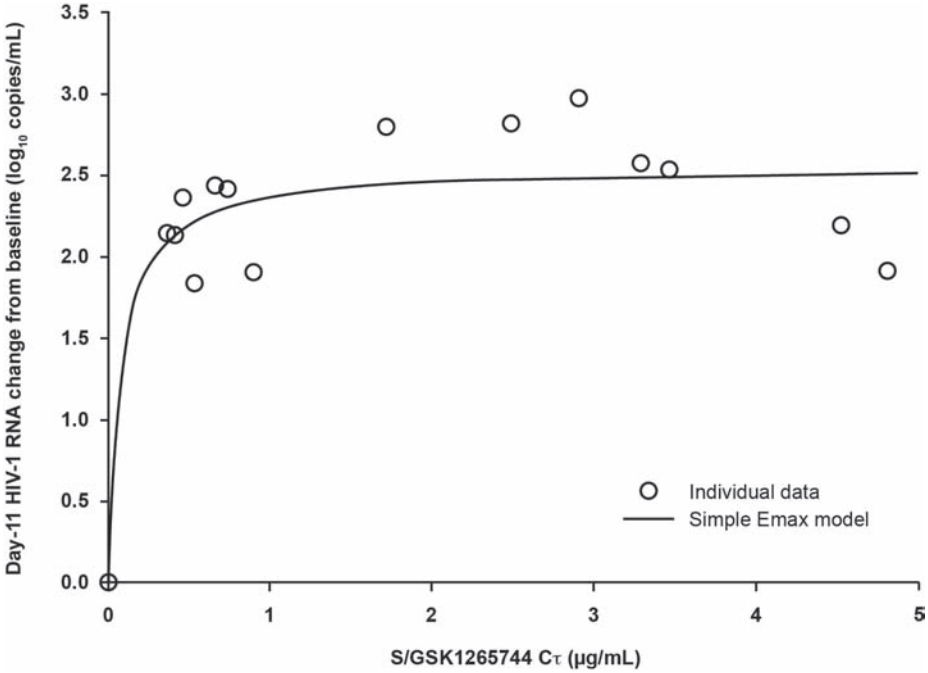

Figure 2. Simple Emax model fit to day 11 change in HIV-1 viral load from baseline versus C_τ. Individual data are represented by *open circles*. C_τ = concentration at the end of the dosing interval; Emax = maximum effect.

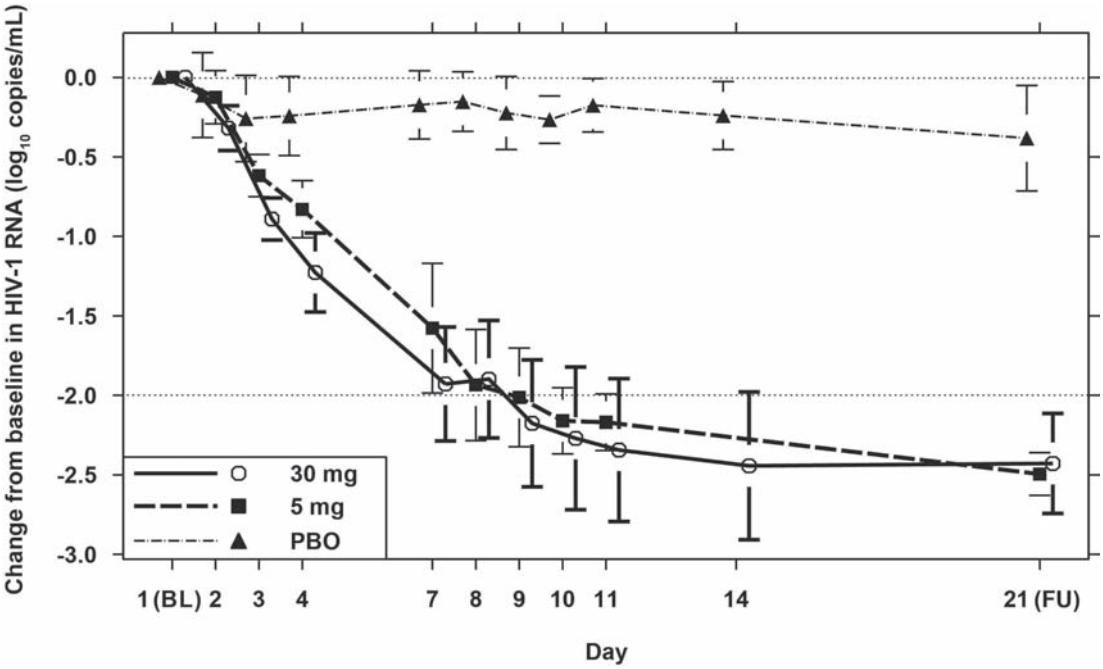

Figure 3. Mean (95% CI) change from baseline in HIV-1 RNA concentration (log_{10} copies/mL) in FTIH study (part C, GSK1265744 30 mg or placebo once daily for 10 days) and phase IIa dose-ranging study (GSK1265744 5 mg or placebo once daily for 10 days). Three-drug antiretroviral therapy was initiated approximately 24 and 96 hours after the last dose of GSK1265744 5 mg and 30 mg, respectively. BL = baseline; FTIH = first time in human; FU = follow-up; PBO = placebo.

Viral Genotyping and Phenotyping

Genotypic and phenotypic data were available for all 11 subjects in the FTIH study on day 1 and for 6 of 11 subjects on day 11. In the phase IIa study, genotypic data were available at baseline (or at screening in 1 subject) and on day 11 for 8 of 9 subjects, while phenotypic data were available for 9 subjects on day 1 and 8 subjects on day 11. Missing data were the result of low plasma HIV-1 RNA concentrations in postdosing samples, leading to an inability to appropriately perform genotypic analysis. None of the subjects in either study had RAL or EVG signature resistance mutations (eg, mutations at codons 138, 140, 148, or 155)[13,14] on day 1 or day 11. The T124A mutation, known as polymorphism[9] and an in vitro passage–selected integrase mutation,[15] was observed in a total of 5 subjects from both studies on day 1; the mutation was still present on day 11 in 1 of the 2 subjects who had a day 11 genotype available. No IN mutations were selected by GSK1265744 for any subject on day 11. In addition, no change in GSK1265744 susceptibility was observed between day 1 and day 11 in either study. There were also no differences in fold change from day 1 to day 11 in either study, with a mean ratio (fold change on day 11 to fold change on day 1) of 1.0 to 1.01 for GSK1265744 and 0.95 to 1.04 for RAL in the phenotypic assay. In addition, there appeared to be no correlations between changes in genotype and changes in phenotype in any subjects.

Safety

No deaths or serious adverse events (SAEs) were reported during any part of either study. In the FTIH study, drug-related AEs were reported in 0 subjects in part A, 6 subjects (20%) in part B (3 in the GSK1265744 5-mg group, 1 in the GSK1265744 25-mg group, and 2 in the placebo group), and 3 subjects (27%) in part C (2 in the GSK1265744 30-mg arm and 1 in the placebo arm). No drug-related AE was grade 3 or 4, and the most frequently reported drug-related AE was headache (n = 5 [8%]). In the phase IIa study, there were no drug-related AEs reported during treatment with GSK1265744 5 mg; the only mild to moderate drug-related AEs were reported in subjects receiving placebo (1 of 2 [50%]) or during the 14 days subjects received 3-drug ART follow-up therapy (1 of 8 [13%]). In the FTIH study, there were no withdrawals due to an AE in part B, whereas there was 1 withdrawal due to an AE in both part A (gingival swelling, toothache, and swollen face) and part C (jaundice during the 3-drug ART phase); neither withdrawal was considered by the investigator to be related to the investigational drug. No discontinuations due to an AE were reported during the phase IIa study.

There were no consistent, clinically significant, or dose-related changes in hematology, clinical chemistry, vital signs, or ECG abnormalities or trends in either study. Three subjects receiving GSK1265744 5 mg (phase IIa study) had clinically relevant laboratory abnormalities. A subject with type I diabetes had grade 2 hyperglycemia at baseline and at all time points other than day 7 (hypoglycemia) and the follow-up visit (grade 3 hyperglycemia). This subject also had grade 2 neutropenia at screening, which peaked at grade 3 on day 10. However, the neutropenia was grade 1 at the follow-up visit, and the subject was asymptomatic throughout the study. On day 7, 1 subject had grade 4 triglyceride elevation subsequent to a very high–fat meal the previous evening, and triglycerides were within normal limits at all other readings. Another subject had grade 2 bilirubin elevation following initiation of 3-drug ART with emtricitabine, tenofovir disoproxil fumarate, and atazanavir/ritonavir.

DISCUSSION

These were the first studies to evaluate the safety, tolerability, and PK profiles of orally administered GSK1265744 in both healthy and HIV-1–infected subjects, as well as the antiretroviral activity of GSK1265744 in HIV-1–infected subjects. Single (up to 50 mg) and repeat (up to 25 mg) doses of GSK1265744 were generally well tolerated in healthy subjects, and doses of 5 mg and 30 mg were well tolerated in HIV-1–infected subjects. No deaths or SAEs were reported, and no clinically significant trends in postdose laboratory abnormalities, vital signs, or ECG values were evident.

The low intersubject PK variability observed with GSK1265744 is consistent with the PK profile of dolutegravir, another INSTI of the same carbamoyl pyridone series of compounds.[16,17] Pharmacokinetic exposure was dose proportional with repeat dosing in both healthy and HIV-1–infected subjects. The day 4 C_{τ} values in healthy subjects were approximately 6-, 14-, and 33-fold above the

in vitro PA-IC_{90} (0.166 µg/mL) for the 5-, 10-, and 25-mg once-daily doses, respectively, supporting further evaluation of once-daily dosing in HIV-1–infected subjects. Plasma exposures of GSK1265744 with tablet dosing were lower than those predicted on the basis of data obtained with administration of the suspension formulation in healthy subjects. However, given that the change was consistent between the 2 studies, this reduction is likely attributable to a formulation effect rather than a population difference. In addition, the mean plasma $t_{1/2}$ of 31.5 hours observed in this study is similar to that of other ARTs with long half-lives such as efavirenz and rilpivirine.[18,19]

There are a number of study limitations. The studies primarily enrolled Caucasian males. In addition, antiviral activity was assessed at only 2 dose levels and did not permit a definitive demonstration of maximal effect. Although the phase IIa study planned to enroll 2 or more dose cohorts to evaluate multiple doses of GSK1265744, drug exposure and antiviral activity results at 5 mg were consistent with predictions, leading the sponsor to conclude the study before enrolling additional dose cohorts. Therefore, data from HIV-1–infected subjects in part C of the FTIH study were combined with data from the phase IIa study to allow assessment of antiviral activity of multiple doses of GSK1265744 in HIV-1–infected subjects. Short-term monotherapy with GSK1265744 (5 and 30 mg) was associated with significant antiviral activity, with a >2.17 $\log_{10}$ mean decline in HIV-1 RNA. This level of antiviral activity is similar to or higher than the treatment response seen in short-term studies of other ARTs, including first-generation INSTIs.[20-26] In addition, 29% and 75% of subjects receiving monotherapy with GSK1265744 5 mg and 30 mg had a plasma HIV-1 RNA concentration <50 copies/mL on days 11 and 14, respectively. The observed high level of antiviral activity, despite GSK1265744 plasma protein binding of >99%, suggests the use of the PA-IC_{90} parameter to estimate the therapeutic target was justified.

No clinically significant genotypic or phenotypic changes were observed in subjects receiving GSK1265744. Although 1 subject had a mutation at codon 124 (T124A) on both day 1 and day 11, this integrase amino acid is known to be polymorphic and is not associated with decreased activity versus INSTIs.[9] GSK1265744 did not select for any mutants associated with clinical resistance to RAL or EVG. Furthermore, no phenotypic resistance to GSK1265744 was observed on day 1 or day 11. After the end of GSK1265744 monotherapy, a multiple-day period of suboptimal plasma concentration for antiviral activity was predicted because of the compound's long plasma half-life. To minimize the possibility of the emergence of drug-resistant viruses during this period, 3-drug ART was administered for at least 14 days, starting on day 14 in the FTIH study (part C) and on day 11 in the phase IIa study.

These results support the continued evaluation of GSK1265744 in HIV-1–infected subjects. GSK1265744 demonstrated potent antiviral activity and the potential for unboosted, low-dose, once-daily oral dosing. In addition to its in vitro resistance profile, the potential to dose monthly to quarterly by intramuscular or subcutaneous injection using a nanosuspension formulation suggests GSK1265744 may be a useful addition to the HIV treatment or prevention armamentarium.

CONCLUSION

An initial clinical evaluation of the HIV INSTI GSK1265744 was performed in healthy and HIV-1–infected adults. The drug was generally well tolerated at all dose levels. Following single and repeat oral dosing, PK analyses confirmed the potential for unboosted, low-dose, once-daily oral administration. In addition, GSK1265744 monotherapy at 5 and 30 mg per day demonstrated potent antiviral activity in HIV-1–infected adults without prior exposure to drugs of the same class. These results support continued clinical development of GSK1265744 and have been used to inform the design of subsequent clinical trials.

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