Drug interaction profile for GSK2248761, a next generation non-nucleoside reverse transcriptase inhibitor

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

• In healthy subjects, GSK2248761 was shown to be safe and well tolerated with single doses up to 1200 mg once daily and with multiple doses up to 800 mg once daily for 7 days. Furthermore, a phase IIa monotherapy study demonstrated that GSK2248761 30 to 800 mg once daily for 7 days was well tolerated in HIV-1-infected subjects and that doses ≥ 100 mg once daily were associated with antiviral activity ($\sim 1.8 \log_{10}$ copies mL^{-1}). However, the potential for drug interactions with co-administration of GSK2248761 and other antiretroviral medications or supportive medications is not known.

WHAT THIS STUDY ADDS

• These studies indicate that GSK2248761 was safe and well tolerated in healthy adults treated in these studies at the doses and duration of therapy evaluated. In addition, these studies indicate that few dosage modifications would be necessary if GSK2248761 were to be administered with most antiretroviral therapies or supportive medications.

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These data were presented in part at the 17th International AIDS Conference, Mexico City, Mexico, August 2008, the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy Meeting, Boston, MA, September 2010, the 18th Conference on Retroviruses and Opportunistic Infections, Boston, MA, February–March 2011 and the 12th International Workshop on Clinical Pharmacology of HIV Therapy, Miami, FL, April 2011.

Keywords

antiretroviral therapy, drug-drug interaction, HIV-1 infection, NNRTI

Received

16 November 2011

Accepted

15 January 2012

Accepted Article Published Online

30 January 2012

AIM

To evaluate potential drug interactions with antiretroviral therapies or supportive therapies for use in conjunction with the once daily, next generation non-nucleoside reverse transcriptase inhibitor GSK2248761 in patients with HIV-1 infection.

METHODS

A series of phase I drug interaction studies was conducted.

RESULTS

GSK2248761 was shown to be a weak CYP3A4 and CYP2D6 inhibitor in a clinical study with a probe cocktail. Mean plasma concentration–time profiles for atazanavir, tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), darunavir (DRV, administered with ritonavir [RTV]), and drosiprenone/ethinylestradiol were similar following co-administration of GSK2248761. Plasma raltegravir AUC(0,∞) and $C_{\max}$ increased by 18% with no change in C_t when raltegravir was co-administered with GSK2248761. Lopinavir (LPV) plasma AUC(0,∞), $C_{\max}$ and C_t decreased by 23%, 14% and 40%, respectively, following administration of lopinavir/ritonavir with GSK2248761. Atorvastatin, rosuvastatin and simvastatin AUC(0,∞) and $C_{\max}$ increased following co-administration with GSK2248761, with the largest changes observed for simvastatin (3.7-fold and 4.3-fold). Changes in maximum and extent of GSK2248761 exposure were marginal after co-administration with atazanavir, TDF/FTC and raltegravir compared with GSK2248761 administered alone. Co-administration of GSK2248761 with DRV/RTV and LPV/RTV increased plasma GSK2248761 exposures by 1.25- to ≤ 2 -fold compared with GSK2248761 administered alone, and increases in GSK2248761 exposure were higher following single dose co-administration of DRV/RTV or LPV/RTV compared with multiple doses. There were few drug-related AEs, and no treatment-related trends in blood chemistry, haematology, urinalysis, vital signs or ECG findings.

CONCLUSIONS

These studies indicate that GSK2248761 was safe and well tolerated in healthy adults treated in these studies at the doses and duration of therapy evaluated.

Introduction

GSK2248761 is a once daily, next generation non-nucleoside reverse transcriptase inhibitor (NNRTI). *In vitro* data indicated GSK2248761 has a different resistance profile from efavirenz and is active against efavirenz-resistant viruses [1]. After GSK2248761 was shown to be safe and well tolerated with single doses up to 1200 mg once daily and with multiple doses up to 800 mg once daily for 7 days in healthy subjects [2], phase IIa monotherapy studies were initiated to investigate the safety and short term efficacy of GSK2248761 in HIV-1-infected subjects. These studies demonstrated that GSK2248761 30 to 800 mg once daily for 7 days was well tolerated in HIV-1-infected subjects [3]. In addition, GSK2248761 in doses of 100 mg once daily or greater achieved mean reductions in viral load of approximately $1.8 \log_{10}$ copies mL^{-1} , and a pharmacokinetic/pharmacodynamic (PK/PD) relationship was identified and characterized. Furthermore, no NNRTI resistance mutations were selected during 7 days of monotherapy with GSK2248761 [4].

Although phase IIb trials of GSK2248761 have since been placed on clinical hold after five reports of seizures in treatment-experienced patients, a series of phase I studies was initially designed to study the safety and potential for drug interactions with co-administration of GSK2248761 and other antiretroviral medications or supportive medications. *In vitro* studies suggested GSK2248761 inhibited human cytochrome P450 (CYP450) enzymes 2C8, 2C9, and 2C19, as well as human organic anion transport protein (OATP1B1 and OATP1B3) [2, 5, 6]. In addition, GSK2248761 demonstrated weak 2D6 and 3A4 inhibition in a clinical study with a probe cocktail [5]. As such, one of the goals of these studies was to examine if GSK2248761 interacts with CYP450 or OATP1B1 substrates (e.g. boosted protease inhibitors, statins). These studies also aimed to examine the potential for two-way interactions between drugs likely to be used in combination with GSK2248761 to treat HIV infection.

Methods

Study designs

A series of phase I trials was conducted between October 2007 and February 2011 (Table 1). Subject eligibility was assessed by physical examination, medical history and laboratory testing. Healthy adult males and females of non-childbearing potential were enrolled in all studies except for the oral contraceptive study, which only enrolled female subjects. Subjects were excluded for a positive HIV or hepatitis C antibody or a positive hepatitis B surface antigen. Subjects were not allowed to receive any prescription or non-prescription drugs, including vitamins or herbal supplements, within 7 days before the first dose and throughout the study. Subjects had a screening visit

within 30 days before the first dose of the study drug and a follow-up visit after the last dose of the study drug. Written informed consent was obtained from all subjects, and the protocol and any amendments were approved by institutional review boards.

Assessments

Safety assessments included monitoring of adverse events (AEs), serious adverse events (SAEs), and concomitant medications, as well as regular checks of clinical chemistry, haematology, urinalysis, vital signs and electrocardiogram (ECG) readings. Serial blood samples for determination of plasma concentrations were collected at appropriate intervals during each study (Table 2). After extraction from plasma by protein precipitation, concentrations of GSK2248761 and concomitant medications were determined by validated, high performance liquid chromatography–tandem mass spectrometry methods. Noncompartmental PK analyses of concentration–time data were performed with WinNonlin® (Pharsight Corporation, St Louis, MO). Parameters included area under the concentration–time curve (AUC), minimum observed plasma concentration ($C_{\min}$), maximum observed plasma concentration ($C_{\max}$), time of occurrence of $C_{\max}$ ($t_{\max}$), concentration at end of dosing interval at steady-state (C_{τ}), apparent oral clearance (CL/F), and apparent terminal elimination phase half-life ($t_{1/2}$). AUC was calculated using the linear-up/log-down trapezoidal method.

Statistical analyses

Statistical analyses were performed on the log-transformed PK parameters, AUC(0, τ), C_{τ} and $C_{\max}$. Analysis of variance was performed using the SAS mixed linear models procedure. The ratio of geometric least squares (GLS) means and associated 90% confidence interval (CI) was estimated for the PK parameters of interest.

Results

Drug interactions with antiretroviral therapies

Atazanavir The mean plasma atazanavir (ATV) concentration–time profiles were similar on day 7 after co-administration of GSK2248761 100 mg or 800 mg with ATV 100 mg (Figure 1). The mean ATV $C_{\max}$ and AUC(0, τ) were 128% to 144% and 111% to 161%, respectively, with GSK2248761 compared with ATV 100 mg alone (Table 3). As expected, ATV concentrations were substantially higher after co-administration of ritonavir (RTV) 100 mg and 100 mg ATV (Figure 1). A single dose design with a low dose of ATV was primarily selected to limit exposure to ATV in healthy volunteers since ATV is an inhibitor of UDP-glucuronyl transferase (UGT) and is associated with increases in unconjugated bilirubin and occasional jaundice [7]. Also, the potential boosting effect of GSK2248761 on ATV is unknown. As such, the extent of exposure after

Table 1

Study designs

Study identifiers	Trial design	Subjects enrolled, N	Description of treatment groups
NV-05A-003	Phase I, randomized, open-label, two period, parallel-group study	18	Group A: ATV 100 mg (day 1), washout (days 2–5), GSK2248761 100 mg (day 6), GSK2248761 100 mg + ATV 100 mg (day 7) Group B: ATV 100 mg (day 1), washout (days 2–5), GSK2248761 800 mg (day 6), GSK2248761 800 mg + ATV 100 mg (day 7) Group C: ATV 100 mg (day 1), washout (days 2–5), RTV 100 mg (day 6), RTV 100 mg + ATV 100 mg (day 7)
NV-05A-004	Phase I, randomized, placebo-controlled, two step, parallel-group study	28	Group A: TDF/FTC (TDF 300 mg + FTC 200 mg) once daily on days 1–14, GSK2248761 800 mg once daily on days 8–14 Group B: GSK2248761-matching placebo* once daily on days 1–7, GSK2248761 800 mg once daily on days 8–14 Group C: Control placebo* once daily on days 1–7, GSK2248761 800 mg once daily on days 8–14
NCT00920088; SGN113045	Phase I, open-label, three-period study	24	Cohort 1: Midazolam 3 mg + dextromethorphan 30 mg (day –2), flurbiprofen 50 mg (day –1), GSK2248761 100 mg once daily (days 1–11), GSK2248761 100 mg + midazolam 3 mg + dextromethorphan 30 mg (day 12), GSK2248761 100 mg + flurbiprofen 50 mg (day 13), GSK2248761 100 mg + LPV/RTV 400/100 mg (day 14), washout (days 15–21), LPV/RTV 400/100 mg twice daily (days 22–28), GSK2248761 once daily† + LPV/RTV 400/100 mg twice daily (days 29–35) Cohort 2: GSK2248761 100 mg once daily (days 1–13), GSK2248761 100 mg + DRV/RTV 600/100 mg (day 14), washout (days 15–21), DRV/RTV 600/100 mg twice daily (days 22–28), GSK2248761 once daily† + DRV/RTV 600/100 mg twice daily (days 29–35)
NCT01101893; SGN113392	Phase I, open-label, three period, fixed-sequence crossover study	15	Period 1: RAL 400 mg twice daily for 5 days followed by a washout period of 5 days Period 2: GSK2248761 200 mg once daily for 5 days Period 3: RAL 400 mg twice daily + GSK2248761 200 mg once daily for 5 days
NCT01138072; SGN113818	Phase I, open-label, single-sequence study	14	Simvastatin 20 mg (day 1), washout (day 2), atorvastatin 20 mg (day 3), washout (days 4–6), rosuvastatin 10 mg (day 7), washout (days 8–9), GSK2248761 200 mg once daily (days 10–14), GSK2248761 200 mg + simvastatin 20 mg (day 15), GSK2248761 200 mg once daily (days 16–17), GSK2248761 200 mg + atorvastatin 20 mg (day 18), GSK2248761 200 mg once daily (days 19–21), GSK2248761 200 mg + rosuvastatin 10 mg (day 22), GSK2248761 200 mg once daily (days 23–24)
NCT01195974; SGN113394	Phase I, randomized, two period, double-blind crossover study‡	10§	Group 1: Ethinylestradiol/drospirenone + GSK2248761 200 mg once daily (days 1–11), ethinylestradiol/drospirenone + placebo once daily (days 12–21) Group 2: Ethinylestradiol/drospirenone + placebo once daily (days 1–11), ethinylestradiol/drospirenone + GSK2248761 200 mg once daily (days 12–21)

ATV, atazanavir; DRV, darunavir; FTC, emtricitabine; LPV, lopinavir; RAL, raltegravir; RTV, ritonavir; TDF, tenofovir disoproxil fumarate. *GSK2248761-matching placebo capsules contained Gelucire® 44/14 (Gattefossé, Saint-Priest, Lyon, France) while control placebo capsules contained microcrystalline cellulose to allow for assessment of potential interactions of GSK2248761 and/or vehicle with thyroid function tests. †GSK2248761 dose was determined during period 1 (i.e. days 1–14). ‡Subjects who were not already on a stable regimen of ethinylestradiol/drospirenone were required to switch to ethinylestradiol/drospirenone for at least 21 days to evaluate tolerability, followed by a washout period of 7 days, before continuing to treatment periods. §Due to the early termination of the study, only 10 subjects completed the study and were included in the pharmacokinetic population.

administration of ATV alone was difficult to estimate and C_{τ} could not be determined for most treatment groups.

After administration of GSK2248761 (100 mg or 800 mg) and ATV 100 mg, increases in peak mean GSK2248761 concentrations were observed compared with GSK2248761 administered alone. Co-administration of GSK2248761 100 mg and 800 mg with ATV resulted in increases in plasma GSK2248761 exposures with AUC(0, τ), $C_{\max}$ and C_{τ} of 65% to 68%, 4% to 26%, and 115% to 236%, respectively (Table 3).

Two subjects (11%) had AEs determined to be potentially related to ATV (one subject with both headache and nausea) and GSK2248761 (headache in one subject). All AEs were mild and transient. No SAEs or deaths were reported and no subject withdrew from the study due to an AE. With the exception of increased mean bilirubin values observed post-study for three subjects in group C (i.e. the group receiving ATV/RTV), there did not appear to be any important treatment-related trends for any labora-

tory parameter. In addition, there were no clinically significant trends in vital signs or ECG readings during study drug dosing.

Tenofovir disoproxil fumarate and emtricitabine Mean plasma concentrations of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) were not significantly altered by co-administration with GSK2248761 compared with TDF/FTC (Gilead Sciences, Inc, Foster City, CA) administered alone (Figure 2A and B). In addition, all plasma TDF and FTC PK parameters were comparable after co-administration of TDF/FTC and GSK2248761 relative to administration of TDF/FTC alone. No interactions were observed between TDF/FTC and GSK2248761 with respect to maximum ($C_{\max}$) and extent (AUC at steady state, AUC_{ss}) of TDF (mean ratios of 114% and 106%, respectively) or FTC exposure (mean ratios of 96% and 106%, respectively).

A lower maximum (mean ratio of 83%) and extent (mean ratio of 80%) of GSK2248761 exposure were

Table 2

Schedule of blood sampling for plasma concentrations

Drug interaction study	Timing of pharmacokinetic sampling (days)
GSK2248761 + atazanavir	<ul style="list-style-type: none"> Atazanavir: 1, 2, 7 and 8* GSK2248761: 6, 7 and 8*
GSK2248761 + TDF/FTC	<ul style="list-style-type: none"> Group A <ul style="list-style-type: none"> TDF/FTC: 1, 4–8 and 11–15 GSK2248761: 1, 8, 11–15 and 16* Groups B/C <ul style="list-style-type: none"> Placebo: 1–7 GSK2248761: 8–14
GSK2248761 + boosted protease inhibitors	<ul style="list-style-type: none"> Cohort 1 <ul style="list-style-type: none"> Probes: –2, –1, 12 and 13 GSK2248761: 7, 14 and 29–35 Lopinavir/Ritonavir: 14 and 22–35 Cohort 2 <ul style="list-style-type: none"> GSK2248761: 1–14 and 29–35 Darunavir/Ritonavir: 14 and 22–35
GSK2248761 + raltegravir	<ul style="list-style-type: none"> Period 1: 2–5 Period 2: 2–5 Period 3: 1–6
GSK2248761 + statins	<ul style="list-style-type: none"> 1–5, 7–9 and 15–25
GSK2248761 + oral contraceptives	<ul style="list-style-type: none"> 8–11 and 19–22

FTC, emtricitabine; TDF, tenofovir disoproxil fumarate. *Or early termination.

Figure 1

Mean plasma concentration vs. time on day 7 for atazanavir (ATV) 100 mg, ATV 100 mg + ritonavir (RTV) 100 mg, ATV 100 mg + GSK2248761 100 mg and ATV 100 mg + GSK2248761 800 mg. ATV (→); ATV + RTV (100 mg) (→); ATV + GSK2248761 (100 mg) (→); ATV + GSK2248761 (800 mg) (→)

observed after co-administration of GSK2248761 and TDF/FTC compared with GSK2248761 alone. Although the 90% confidence intervals of the ratio of the geometric means for GSK2248761 C_{max} and AUC_{ss} were not completely contained within the predefined critical range, the 90% confidence intervals were wide, indicating low precision for this comparison. The variability associated with GSK2248761 exposure was unexpectedly high due in part to one subject in group C whose exposure was approximately 2- to 3-fold higher compared with the median values for

$AUC(0,\tau)$ and C_{max} (there was an approximately 20% lower maximum and overall extent of GSK2248761 exposure after administration of GSK2248761 and TDF/FTC compared with GSK2248761 alone).

Seventy-six AEs were reported, most occurring before exposure to GSK2248761 (79%). The most common AE was headache (reported by 25% of subjects). The majority of AEs were mild (82%) and there were no SAEs or deaths in the study. Three subjects discontinued because of AEs before exposure to GSK2248761 (two for rash/pruritus and vomiting possibly related to TDF/FTC and one because of an infected insect bite requiring concomitant medications). There were no treatment-related trends in blood chemistry, haematology, urinalysis, vital signs or ECG findings. Although GSK2248761 could affect thyroid function, most thyroid function variables remained within normal limits, and no subjects experienced clinically significant abnormal values for any thyroid function parameter.

Raltegravir Co-administration of GSK2248761 200 mg once daily and raltegravir (RAL) 400 mg twice daily did not result in clinically significant PK interactions (Figure 3). A decrease in plasma RAL $AUC(0,\tau)$ and C_{max} of 18% (90% CI of 0.555, 1.20 and 0.482, 1.38, respectively) and no change in $C\tau$ were observed when RAL 400 mg twice daily was co-administered with GSK2248761 200 mg once daily (Table 4). Co-administration of RAL with GSK2248761 resulted in mean increases in plasma GSK2248761 $AUC(0,\tau)$, C_{max} and $C\tau$ of 15%, 16% and 13%, respectively (Table 4).

The most frequently reported AE was nausea, occurring in three subjects receiving GSK2248761 alone (only one instance was determined to be drug related). All AEs were mild. There were no SAEs or deaths reported and no subjects discontinued the study due to an AE. In addition, there were no clinically significant changes in vital signs or ECG findings, and no clinical laboratory values were reported during the study as AEs.

CYP450 probes and boosted protease inhibitors Co-administration of metabolic probes with repeat doses of GSK2248761 100 mg resulted in increases in midazolam and dextromethorphan $AUC(0,\infty)$ of 54% and 83%, respectively. No changes were observed in plasma flurbiprofen $AUC(0,\infty)$ or in the 4-OH flurbiprofen $AUC(0,24\text{ h})$: flurbiprofen $AUC(0,24\text{ h})$ ratio (i.e. metabolite: parent compound ratio).

When darunavir/ritonavir (DRV/RTV) 600/100 mg twice daily was administered with GSK2248761 100 mg once daily, there were no effects on DRV pharmacokinetics (decreases in maximum and extent of DRV exposure of 5%) or on plasma RTV exposure (increases in maximum and extent of RTV exposure of 2%). However, co-administration of lopinavir/ritonavir (LPV/RTV) 400/100 mg twice daily with GSK2248761 100 mg once daily was associated with decreases in plasma LPV $AUC(0,\tau)$, C_{max} and $C\tau$ (23%, 14%

Table 3

Summary of treatment comparisons for GSK2248761 and atazanavir

Plasma parameter	GLS mean ratio (90% CI)				
	GSK2248761 100 mg + ATV vs. ATV	ATV GSK2248761 800 mg + ATV vs. ATV	RTV 100 mg + ATV 100 mg vs. ATV	GSK2248761 100 mg + ATV vs. GSK2248761	GSK2248761 GSK2248761 800 mg + ATV vs. GSK2248761
AUC(0,τ)	1.11 (0.80, 1.54)	1.61 (1.07, 2.41)	25.88 (17.87, 37.50)	1.65 (1.42, 1.91)	1.68 (1.31, 2.14)
C _{max}	1.28 (0.87, 1.88)	1.44 (0.92, 2.27)	15.18 (11.55, 19.96)	1.04 (0.97, 1.12)	1.26 (1.09, 1.45)
C _τ	–	–	–	3.36 (2.34, 4.82)	2.15 (1.68, 2.77)

ATV, atazanavir; AUC(0,τ), area under the concentration–time curve; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_τ, concentration at end of dosing interval at steady state; GLS, geometric least squares; RTV, ritonavir.

Figure 2

Mean plasma concentration vs. time on day 14 for (A) tenofovir disoproxil fumarate (TDF) and (B) emtricitabine (FTC) each alone and with GSK2248761. (A) TDF (—■—); TDF + GSK2248761 (---▲---). (B) FTC (—■—); FTC + GSK2248761 (---▲---).

and 40%, respectively), while plasma RTV AUC(0,τ), C_{max} and C_τ were decreased by 19%, 21% and 42%, respectively.

Co-administration of single and repeat doses of DRV/RTV or LPV/RTV with GSK2248761 increased plasma GSK2248761 exposures compared with GSK2248761

administered alone (Table 5). In general, the increases in plasma GSK2248761 exposure were less than 2-fold, and GSK2248761 exposure increased more with single dose co-administration of LPV/RTV or DRV/RTV than with co-administration of repeat doses of LPV/RTV or DRV/RTV.

Overall, 11 subjects (46%) experienced drug-related AEs. All drug-related AEs were mild to moderate, with diarrhoea, somnolence and headache being the most common. Three subjects withdrew from the study due to AEs, one of which was possibly related to the study drug (GSK2248761 + LPV/RTV). There were no clinically significant changes in laboratory tests, vital signs or ECG parameters.

Drug interactions with supportive medications

Statins Mean plasma concentrations of select statins and statin metabolites when statins were administered alone or with GSK2248761 are presented in Figure 4. Co-administration of GSK2248761 200 mg once daily with a single dose of atorvastatin 20 mg or rosuvastatin 10 mg increased AUC(0,∞) and C_{max} by approximately 40% and 30%, respectively, relative to either statin alone (Table 6). However, the increase in atorvastatin PK parameters was offset by commensurate decreases in ortho-hydroxy atorvastatin PK parameters. Simvastatin AUC(0,∞) and C_{max} increased 3.7-fold and 4.3-fold, respectively, after co-administration of simvastatin with GSK2248761 relative to simvastatin alone.

Two subjects experienced mild drug-related AEs, but there were no SAEs, deaths or withdrawals due to AEs. In addition, there were no treatment-related laboratory findings or clinically significant changes in vital signs or ECG readings.

Oral contraceptives Ten subjects completed the study and were included in the PK summary population. In those subjects, an increase in plasma drospirenone AUC(0,τ), C_{max} and C_{min} of 18% to 22% was observed when ethinylestradiol/drospirenone (Bayer HealthCare Pharmaceuticals, Inc, Leverkusen, Germany) was co-administered with GSK2248761, whereas no changes in plasma

Figure 3

Mean plasma concentration vs. time for (A) GSK2248761 200 mg once daily alone and with raltegravir (RAL) 400 mg twice daily and (B) raltegravir 400 mg twice daily alone and with GSK2248761 200 mg once daily. (A) GSK2248761 ($\blacktriangle$); GSK2248761 + RAL ($\blacksquare$). (B) RAL ($\blacktriangle$); GSK2248761 + RAL ($\blacksquare$)

Table 4

Plasma GSK2248761 and raltegravir pharmacokinetic treatment comparisons

Pharmacokinetic parameter	GSK2248761 GLS mean ratio (90% CI)	Raltegravir GLS mean ratio (90% CI)
	GSK2248761 + raltegravir vs. GSK2248761	GSK2248761 + raltegravir vs. raltegravir
AUC(0, τ)	1.15 (1.04, 1.26)	0.82 (0.56, 1.20)
$C_{\max}$	1.16 (1.05, 1.28)	0.82 (0.48, 1.38)
C_t	1.13 (1.03, 1.25)	1.04 (0.82, 1.32)

AUC(0, τ), area under the concentration–time curve; CI, confidence interval; $C_{\max}$, maximum observed plasma concentration; C_t , concentration at end of dosing interval at steady state; GLS, geometric least squares.

ethinylestradiol AUC(0, τ) and $C_{\max}$ were observed. Furthermore, no differences in maximum luteinizing hormone or follicle-stimulating hormone concentrations between the two treatments were observed.

Three AEs were considered drug related (one report of headache in both the ethinylestradiol/drospirenone + GSK2248761 and the ethinylestradiol/drospirenone alone groups and one report of upper abdominal pain in the

Table 5

Plasma GSK2248761 pharmacokinetic treatment comparisons

Pharmacokinetic parameter	Cohort 1	Cohort 2		
	GLS mean ratio (90% CI) GSK2248761 + LPV/RTV SD vs. GSK2248761	GSK2248761 + LPV/RTV RD vs. GSK2248761	GLS mean ratio (90% CI) GSK2248761 + DRV/RTV SD vs. GSK2248761	GSK2248761 + DRV/RTV RD vs. GSK2248761
AUC(0,τ)	1.97 (1.62, 2.40)	1.25 (1.00, 1.56)	1.93 (1.66, 2.24)	1.41 (1.07, 1.86)
C _{max}	1.43 (1.14, 1.80)	1.23 (1.03, 1.47)	1.50 (1.30, 1.74)	1.34 (1.12, 1.60)
C _τ	0.97 (0.85, 1.11)	1.61 (1.09, 2.39)	1.10 (1.00, 1.20)	1.58 (1.09, 2.29)

AUC(0,τ), area under the concentration–time curve; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_τ, concentration at end of dosing interval at steady state; DRV, darunavir; GLS, geometric least squares; LPV, lopinavir; RD, repeat dose; RTV, ritonavir; SD, single dose.

ethinylestradiol/drospirenone alone group). There were no SAEs, withdrawals due to AEs or deaths. All AEs were mild to moderate, except one instance of severe diarrhoea in a patient receiving ethinylestradiol/drospirenone alone (resolved in ~24 h, not considered treatment related). There were no grade 3 or 4 treatment-emergent laboratory values and no clinically significant vital sign values or ECG abnormalities were observed.

Discussion

This series of drug interaction studies evaluated the potential for interactions between GSK2248761 (up to 800 mg) and a variety of antiretroviral therapies and supportive medications in healthy adult subjects. A marginal drug interaction effect was noted on ATV PK after administration of GSK2248761, with mean ratios of C_{max} and AUC(0,τ) indicating an 11% to 61% higher maximum and overall extent of ATV exposure following combination therapy compared with administration of ATV 100 mg alone. There was a moderate, but not likely to be clinically meaningful, drug interaction effect on the overall extent of GSK2248761 exposure [percent mean ratio for AUC(0,τ) of 165%–168%] and minimum GSK2248761 concentrations (percent mean ratio for C_τ of 215%–336%) after co-administration of ATV with either GSK2248761 100 mg or 800 mg. By contrast, ATV had only a slight effect on the maximum exposure of GSK2248761 100 mg or 800 mg. Available data suggest that GSK2248761 is primarily metabolized through oxidation and to a lesser extent through conjugation (e.g. glucuronidation). Thus, the increase in GSK2248761 exposure is likely attributable to the inhibitive effects of ATV on both CYP450 3A and UGT1A1 [8, 9].

There was no drug interaction between GSK2248761 and TDF/FTC with respect to TDF and FTC. However, this study may not have been adequately powered to assess conclusively drug interaction with respect to GSK2248761 because of the high variability of PK parameters for GSK2248761. In addition, the higher median C_{max} and AUC(0,τ) noted for one subject in group C may have

skewed the data towards an indication of a drug interaction. Regardless, the data indicated no apparent dose– or exposure–response relationship within the dose range covered in this study, suggesting the marginal change in exposure was unlikely to be clinically relevant.

As RAL does not inhibit CYP3A or UGT1A1, RAL was not expected to alter plasma GSK2248761 exposure, and the marginal increases in plasma GSK2248761 exposure observed when GSK2248761 was co-administered with RAL were not clinically significant. Since RAL is eliminated through UGT1A1 metabolism and GSK2248761 had been demonstrated to inhibit UGT1A1 in vitro (IC₅₀ = 2.8 μM; data not shown), it was possible that co-administration of GSK2248761 could increase RAL exposure. Consistent with many drug-drug studies, RAL was associated with large intersubject variability (i.e. 90% CIs of the geometric least square mean ratios for PK parameters were wide). However, the changes observed in RAL PK when co-administered with GSK2248761 were not clinically significant. Thus, no RAL dosage adjustments are required when RAL is co-administered with GSK2248761.

The increases in midazolam and dextromethorphan AUC(0,τ) of 50% to 80% when each was co-administered with GSK2248761 indicate that GSK2248761 is a weak CYP3A4 and CYP2D6 inhibitor, while the lack of effect of flurbiprofen suggests GSK2248761 does not affect CYP2C9 activity. These data confirm the findings of the phase I trial with ATV and suggest GSK2248761 has low drug interaction potential when co-administered with other drugs that are primarily metabolized through CYP450. Given that midazolam, DRV and LPV are all predominantly metabolized by CYP3A4, the decrease in LPV exposure is inconsistent with the increased midazolam exposure and lack of change in the DRV/RTV exposure. At this time, the mechanism involved in the reduced LPV/RTV concentrations observed with GSK2248761 co-administration is unknown, and the clinical significance of this interaction remains to be determined. The greater increase in exposure of GSK2248761 after a single dose than after repeated doses may have occurred because the inhibition of CYP3A4 or other enzymes/transporters was counteracted by

Figure 4

Mean plasma concentration vs. time for (A) simvastatin and simvastatin acid, (B) atorvastatin and ortho-hydroxy atorvastatin (inset of first 12 h post dose) and (C) rosuvastatin each alone and with GSK2248761. (A) Simvastatin (■); Simvastatin + GSK2248761 (▲). (B) Atorvastatin (■); Atorvastatin + GSK2248761 (▲). (C) Rosuvastatin (■); Rosuvastatin + GSK2248761 (▲).

Table 6

Summary of effects of GSK2248761 on pharmacokinetics of select statins

Analyte (treatment comparison)	GLS mean ratio (90% CI) AUC(0,∞)	AUC(0,48 h)	C _{max}	t _{1/2}
Simvastatin (D vs. A)	3.73 (2.89, 4.82)	3.74 (2.91, 4.82)	4.33 (3.07, 6.10)	1.15 (0.88, 1.51)
Simvastatin acid (D vs. A)	2.51 (1.89, 3.34)	2.95 (2.43, 3.58)	3.90 (3.12, 4.88)	0.74 (0.59, 0.92)
Atorvastatin (E vs. B)	1.50 (1.29, 1.75)	1.47 (1.26, 1.70)	1.25 (0.91, 1.72)	1.22 (1.01, 1.47)
Ortho-hydroxy atorvastatin (E vs. B)	0.83 (0.75, 0.91)	0.76 (0.68, 0.84)	0.41 (0.30, 0.55)	1.69 (1.43, 1.99)
Rosuvastatin (F vs. C)	1.35 (1.22, 1.48)	1.26 (1.15, 1.39)	1.32 (1.20, 1.45)	1.59 (1.32, 1.91)

AUC(0,∞), area under the concentration–time curve; CI, confidence interval; C_{max}, maximum observed plasma concentration; GLS, geometric least squares; t_{1/2}, terminal elimination phase half-life. Treatment A: simvastatin 20 mg (single dose). Treatment B: atorvastatin 20 mg (single dose). Treatment C: rosuvastatin 10 mg (single dose). Treatment D: GSK2248761 200 mg once daily + simvastatin 20 mg (single dose). Treatment E: GSK2248761 200 mg once daily + atorvastatin 20 mg (single dose). Treatment F: GSK2248761 200 mg once daily + rosuvastatin 10 mg (single dose).

induction of these enzymes/transporters after repeat dosing. These increases in GSK2248761 are not considered clinically significant because GSK2248761 doses up to 800 mg once daily have been administered to HIV-infected subjects without clinically significant drug-related side effects. Thus, no GSK2248761 dosage adjustments are required when co-administered with DRV/RTV or LPV/RTV.

Several antiretroviral agents that affect CYP3A4 are known to influence statin exposure. Efavirenz, a mixed inducer/inhibitor of CYP3A4, was associated with ≥40% reductions in atorvastatin, pravastatin and simvastatin exposure [10], while protease inhibitor boosters, such as ritonavir and saquinavir, have been shown to increase exposure of atorvastatin by 79% and simvastatin by up to 3000% [11]. Due to the magnitude of potential inhibition of simvastatin metabolism (and the resultant risk for rhabdomyolysis), drugs that inhibit CYP3A4 are not recommended for co-administration with simvastatin [12]. In these studies, co-administration of GSK2248761 with atorvastatin, rosuvastatin and simvastatin was shown to increase significantly the exposure of these statins. Simvastatin was the most sensitive to inhibition by GSK2248761, consistent with trends noted for other antiretroviral therapies that inhibit CYP3A4. The net atorvastatin-related inhibition by GSK2248761 was minimal as the increases in atorvastatin exposure were potentially offset by decreases in exposure of ortho-hydroxy atorvastatin, the CYP3A4 mediated active metabolite of atorvastatin. Exposures of rosuvastatin were increased by 26% to 32% after co-administration with GSK2248761 relative to rosuvastatin alone. Therefore, atorvastatin and rosuvastatin would be preferable to simvastatin for the treatment of hyperlipidaemia in patients receiving GSK2248761 for HIV-1 infection, and monitoring of AEs related to increases in any HMG-CoA reductase inhibitor (e.g. rhabdomyolysis) is warranted.

Although the oral contraceptive study evaluated a lower number of patients than originally planned because of the early study termination, there were no changes in PK of ethinylestradiol when co-administered with

GSK2248761. Increases in drospirenone plasma AUC(0,∞) and C_{max} when ethinylestradiol/drospirenone was co-administered with GSK2248761 (~18%) were not considered to be clinically meaningful or to require dose modification. Furthermore, changes in hormonal markers in this limited population were minimal.

Although the development of GSK2248761 has been placed on clinical hold, these studies demonstrate that GSK2248761 was safe and well tolerated in healthy adults at the doses and duration of therapy evaluated. In addition, these studies indicate that few dosage modifications would be necessary if GSK2248761 were to be administered with most antiretroviral therapies or supportive medications (Table 7).

Competing Interests

All authors are employed by and may receive company stock as part of their incentive packages from either Glaxo-SmithKline (de Serres, Gould, Johnson, Kim, Lou, Piscitelli and White) or Idenix Pharmaceuticals, Inc (Pietropaolo, Mayers and Zhou). All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.

The authors would like to acknowledge the following principal investigators and Clinical Research Unit Staff: Robert A. Blum, PharmD, Buffalo Clinical Research Center; Gregory M. Haugen, MD, Cetero Research, Azra Hussaini, MD, Parexel Baltimore Early Phase Clinical Unit, Matthew M. Medlock, MD, PPD Development and Grant Generaux, Michael Leonard, and Lindsey Webster, Preclinical Drug Metabolism and Pharmacokinetics, GlaxoSmithKline. The authors also wish to acknowledge the following individual for his editorial assistance during the development of this manuscript: Todd Parker.

Funding for these studies was provided by GlaxoSmithKline Pharmaceuticals, LLC and Viiv Healthcare.

Table 7

Overview of dosing recommendations

Drug interaction study	Dosing recommendation(s)
GSK2248761 + atazanavir	<ul style="list-style-type: none"> No GSK2248761 dosage adjustments are necessary when GSK2248761 is co-administered with atazanavir
GSK2248761 + TDF/FTC	<ul style="list-style-type: none"> No dosage adjustments are necessary for TDF/FTC or GSK2248761 when co-administered
GSK2248761 + raltegravir	<ul style="list-style-type: none"> No dosage adjustments are necessary for raltegravir or GSK2248761 when co-administered
GSK2248761 + boosted protease inhibitors	<ul style="list-style-type: none"> No GSK2248761 dosage adjustments are necessary when GSK2248761 is co-administered with DRV/RTV or LPV/RTV No DRV/RTV dosage adjustments are necessary when GSK2248761 is co-administered with DRV/RTV Potential interactions of LPV/RTV with GSK2248761 require further study before LPV/RTV dosage recommendations can be provided
GSK2248761 + statins (atorvastatin, rosuvastatin and simvastatin)	<ul style="list-style-type: none"> GSK2248761 should be used with caution with simvastatin doses >40 mg
GSK2248761 + oral contraceptives	<ul style="list-style-type: none"> No dosage adjustments are necessary for ethinylestradiol/drospirenone when co-administered with GSK2248761

DRV, darunavir; FTC, emtricitabine; LPV, lopinavir; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

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