The effect of CYP3A inhibitors and inducers on the pharmacokinetics of telaprevir in healthy volunteers

Varun Garg,¹ Gurudatt Chandorkar,^{2*} Yijun Yang,^{3*} Nathalie Adda,¹ Lindsay McNair,^{4*} Katia Alves,¹ Frances Smith¹ & Rolf P. G. van Heeswijk⁵

¹Vertex Pharmaceuticals Incorporated, Cambridge, MA, ²Cubist Pharmaceuticals, Inc., Lexington, MA, ³Accelaron Pharma, Inc., Cambridge, MA, ⁴Equipose Consulting LLC, Allston, MA, USA and ⁵Janssen Infectious Diseases BVBA, Beerse, Belgium

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Telaprevir is a hepatitis C virus protease inhibitor for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease. *In vitro* studies indicated that CYP3A was the major cytochrome P-450 (CYP) isozyme involved in the metabolism of telaprevir. It is important to understand the potential for drug–drug interactions of telaprevir when it is co-administered with CYP3A inhibitors or inducers.

WHAT THIS STUDY ADDS

- CYP3A inducers, rifampicin and efavirenz, can reduce telaprevir exposure to varying degrees based on their potency. After a single dose, telaprevir exposure is increased when ketoconazole, a strong CYP3A inhibitor, is co-administered. However, at steady-state, telaprevir exposure is less likely to be affected by CYP3A inhibitors.

Correspondence

Dr Varun Garg PhD, Vertex Pharmaceuticals Incorporated, 130 Waverly Street, Cambridge, Massachusetts 02139-4242, USA.
Tel: +1 617 444 6757
Fax: +1 617 444 7166
E-mail: varun_garg@vrtx.com

*Employed by Vertex during this study.

Keywords

CYP3A4, drug interaction, HCV, pharmacokinetics and drug metabolism, telaprevir

Received

5 October 2011

Accepted

20 May 2012

Accepted Article Published Online

29 May 2012

AIM

To evaluate the effects of ketoconazole, rifampicin and efavirenz on the pharmacokinetics of telaprevir in healthy volunteers.

METHOD

Results from three clinical studies are described. (1) Volunteers received a single 750 mg dose telaprevir with and without a single 400 mg dose ketoconazole. (2) Volunteers received (a) 1250 mg telaprevir followed by three 750 mg doses given every 8 h and (b) four 1250 mg telaprevir doses given every 8 h, with a single 400 mg dose ketoconazole given with the fourth dose of telaprevir. (3) Volunteers received either a single 750 mg dose telaprevir with or without 600 mg once daily rifampicin, or 750 mg every 8 h telaprevir with and without 600 mg once daily efavirenz.

RESULTS

A single 400 mg dose of ketoconazole increased single dose telaprevir exposure: the geometric least-squares mean ratio (GLSMR, with 90% confidence limits) was 1.24 (1.10, 1.41) for C_{max} and 1.62 (1.45, 1.81) for AUC(0,∞). However, after multiple doses of telaprevir, there was no discernible effect of ketoconazole on telaprevir exposure. Co-administration of rifampicin at steady-state markedly reduced single dose telaprevir exposure with GLSMRs of 0.14 (0.11, 0.18) for C_{max} and 0.08 (0.07, 0.11) for AUC(0,∞), whereas efavirenz had a smaller effect on telaprevir exposure when both drugs were co-administered at steady-state, with GLSMRs of 0.91 (0.81, 1.02) for C_{max} , 0.53 (0.44, 0.65) for C_{min} , and 0.74 (0.65, 0.84) for AUC(0,8 h).

CONCLUSION

CYP3A inducers, rifampicin and efavirenz, can reduce telaprevir exposure to varying degrees based on their potency. The effect of ketoconazole as an inhibitor of telaprevir metabolism is more pronounced after a single dose of telaprevir than after repeated administration.

Introduction

Telaprevir is an orally bioavailable inhibitor of the non-structural 3/4A (NS3/4A) hepatitis C virus (HCV) protease [1]. In recent phase 2 and phase 3 studies, telaprevir (750 mg three times a day) in combination with pegylated interferon (Peg-IFN) and ribavirin (RBV) in patients with genotype 1 chronic hepatitis C infection, significantly increased the rates of sustained virologic response [2–7]. Telaprevir was recently approved in the USA, Canada, Europe and Japan for the treatment of genotype 1 chronic hepatitis C in combination with pegylated interferon (Peg-IFN) and ribavirin (RBV) in adult patients with compensated liver disease [8–11].

Telaprevir is extensively metabolized via hydrolysis, oxidation and reduction, and *in vitro* studies indicate that the major cytochrome P-450 (CYP) isozyme involved in the metabolism of telaprevir is CYP3A [8–11]. Therefore, the potential for drug–drug interactions of telaprevir when it is co-administered with the CYP3A inhibitor, ketoconazole, or with CYP3A inducers, rifampicin or efavirenz, were evaluated in three clinical studies.

Methods

Volunteers

The protocol and informed consent form were approved by the relevant ethics committee for each study in accordance with national procedures. All volunteers provided written informed consent before participating in a study. All studies were conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and local laws and regulations.

Study design

Results taken from three different clinical studies (studies 003, 008 and 016) relevant to CYP3A inducers and inhibitors are summarized. Volunteers were to end any short duration courses of prescription medications at least 14 days before the screening visit and over the counter medication on the date of the screening visit. Volunteers were to have stopped consumption of herbal medications, dietary supplements (e.g. St John's Wort, *Ginkgo biloba*, garlic supplements), vitamins, grapefruit or grapefruit juice, apple juice or orange juice within 14 days before the first administration of study drug and were not to have consumed these items until the last pharmacokinetic (PK) sample following the last dose of study drug. Volunteers were not allowed to consume any alcohol from 72 h before study drug administration through the follow-up visit. Volunteers were not to consume any caffeinated beverages during the in-house periods and were advised to consume no more than five to seven cups of caffeinated beverages per day during the outpatient period.

In study 003, the effect of a single dose of ketoconazole on telaprevir single dose PK was studied. This was a randomized, open-label, single dose, crossover study. Volunteers ($n = 17$) received either a single oral dose of 750 mg of telaprevir alone, followed by single doses of 750 mg of telaprevir with 400 mg of ketoconazole, or the same regimens but in the opposite order. Telaprevir, or telaprevir and ketoconazole administered simultaneously, were administered following a standard (normal caloric) breakfast.

In Study 008, ketoconazole was used in an attempt to increase telaprevir exposure in comparing the effect of therapeutic and supratherapeutic systemic exposures of telaprevir on QT_c prolongation. Only the PK results of this study relevant to CYP3A inhibition are included in this manuscript. The study was a randomized, placebo-controlled, four regimen, four period crossover study ($n = 89$). The two dosing regimens to be discussed here are 1) telaprevir administered as 1250 mg dose followed by three 750 mg doses given every 8 h and 2) telaprevir administered as four 1250 mg doses given every 8 h, with a single dose of 400 mg ketoconazole given with the fourth dose of telaprevir. All doses were orally administered after a standardized meal or snack. A washout period of at least 5 days occurred between each subsequent period.

In study 016, the effect of rifampicin, a strong CYP3A4 inducer, and efavirenz, a moderately strong inducer of CYP3A, on the single dose (rifampicin) and steady-state (efavirenz) PK of telaprevir was evaluated. This was an open label, single sequence, non-randomized study in which volunteers were assigned to one of two treatment parts: Part 1 (16 volunteers) evaluated the effects of multiple doses of rifampicin on the single dose PK of telaprevir and part 2 (28 volunteers) evaluated the multiple dose interaction between telaprevir and efavirenz. In part 1, a single 750 mg dose of telaprevir was administered after a standardized breakfast on two occasions (days 1 and 9), with co-administration of 600 mg once daily rifampicin 3.5 h after breakfast for 8 days (days 2–9). The PK of telaprevir were evaluated on day 1 (telaprevir alone) and on day 9 (co-administered with rifampicin). In part 2, telaprevir 750 mg every 8 h was administered after a snack or meal for 10 days on two separate occasions (days 1–10 and days 28–37). The PK of telaprevir were evaluated on day 10 (telaprevir alone) and on day 37 (co-administered with efavirenz). Efavirenz (600 mg once daily) was administered 3.5 h after the start of breakfast for 20 consecutive days (from study days 18–37). PK of efavirenz was evaluated on day 27 (efavirenz alone) and on day 37 (co-administered with telaprevir).

Drugs administered

The following drugs were used in this study: telaprevir 250 mg tablets (Panthion, Mississauga, ON, Canada), ketoconazole 200 mg tablets (study 008: Pliva, East Hanover, New Jersey, USA; study 003: Nizoral®, Janssen Pharmaceutica Products, L.P., New Jersey, USA), rifampicin 300 mg cap-

sules (Eon Labs, Laurelton, New York, USA) and efavirenz 600 mg tablets (Sustiva®, Bristol-Myers Squibb, Princeton, New Jersey, USA).

A designated staff member observed all dosing during the inpatient periods of each study, and a visual check of each subject's hands and mouth was performed after administration of study drug. During out-patient periods, compliance was assessed by counting returned dosage units and reviewing the drug dosing logs for the study drug regimen. No volunteers were withdrawn due to non-compliance in these studies.

Bioanalytical methods

Telaprevir, ketoconazole, rifampicin, and efavirenz were analyzed by fully validated LC/MS/MS methods. The inter-assay precision and accuracy were well within the pre-specified criteria for acceptability of the assays based on the FDA's guidance for bioanalytical assay validation [12].

The telaprevir bioanalytical method was described previously [13]. Briefly, telaprevir and its internal standard d11-VX-950, ketoconazole and its internal standard, ketoconazole-d3, and efavirenz and its internal standard efavirenz-d4, were extracted from human plasma by liquid-liquid extraction. After evaporation under nitrogen, the residue was reconstituted and analyzed using liquid chromatography (LC; normal phase) with tandem mass spectrometric detection (MS/MS). Rifampicin and the internal standard, rifabutin, were extracted from human plasma by solid phase extraction (SPE). The SPE eluent was analyzed using LC with MS/MS.

The standard curve range was from 2.00 to 1000 ng ml⁻¹ or 20.0 to 5000 ng ml⁻¹ for telaprevir, 5.00 to 1000 ng ml⁻¹ (in study 008) and 5.00 to 10 000 ng ml⁻¹ (in study 003) for ketoconazole, 1.00 to 1000 ng ml⁻¹ for efavirenz, and 50.0 to 35 000 ng ml⁻¹ for rifampicin.

Pharmacokinetic analyses

PK analyses were carried out using WinNonlin, Version 5.1.1 (Pharsight Corporation, Mountain View, California, USA). PK

parameters were determined using standard noncompartmental methods and summarized for each regimen. PK data were not always available for all volunteers (due to discontinuation), and the number of volunteers from which PK data were obtained for each analysis is given in the relevant tables and figure legends.

The terminal slope, λ_z , was computed by linear regression of the terminal linear portion of the log concentration vs. time data. The apparent elimination half-life ($t_{1/2}$) was calculated as $\ln(2)/\lambda_z$. Area under the curve (AUC) was computed using the linear trapezoidal rule between increasing concentrations and the logarithmic trapezoidal rule between decreasing concentrations. For PK after a single dose, the AUC was extrapolated to infinity. For PK at steady-state, the AUC was calculated for the dosing interval.

Analysis of variance (ANOVA), with dosing regimen as an effect, was performed on the log-transformed maximum observed plasma concentrations (C_{max}) and AUC data using the general linear model procedure in SAS, Version 8.2 (SAS Institute, Cary, North Carolina). The 90% confidence intervals (CIs) were calculated for the ratios of geometric least-squares means (GLSMR) of C_{max} and AUC. No relevant drug interaction was concluded if the 90% CI for the ratios of the two dosing regimens was within the no effect range of 0.80 to 1.25 [14].

Safety assessments and analysis

Adverse events, vital signs and 12-lead electrocardiograms (ECGs), clinical chemistry, haematology and physical examinations were monitored during these clinical studies. A follow-up visit was conducted 5 to 14 days following the last dose of study drug in each study.

Results

Demographics

Table 1 shows demographics for each of the three studies discussed.

Table 1

Summary of demographic data and baseline characteristics

Variable	Study 003	Study 008	Study 016	
			Part 1	Part 2
Gender, n (%)				
Male	35 (100)	89 (100)	13 (81)	27 (96)
Female	–	–	3 (19)	1 (4)
Race, n (%)				
Asian	1 (3)	3 (3)	1 (6)	–
Black or African American	5 (14)	15 (17)	2 (12)	6 (21)
Caucasian or White	28 (80)	70 (78)	13 (81)	19 (68)
Other	1 (3)	1 (1)	–	3 (11)
Age (years) median (min, max)	30 (19, 55)	27 (18, 54)	36.5 (22, 58)	24.5 (20, 52)
BMI (kg m ⁻²) median (min, max)	25.9 (21.2, 29.4)	25.3 (19.7, 30.6)	25.1 (20.8, 31.6)	26.3 (20.4, 31.5)

Data for age and body mass index (BMI) are presented as median (range).

Effect of ketoconazole on the pharmacokinetics of telaprevir

The mean plasma telaprevir concentration vs.time profiles after a single dose of 750 mg telaprevir administered alone or co-administered with a single dose of 400 mg ketoconazole are shown in Figure 1 and the PK parameters are summarized in Table 2 (results from study 003). Upon co-administration with ketoconazole, both C_{max} and $AUC(0,\infty)$ of telaprevir increased 1.24-fold for C_{max} and 1.62-fold for $AUC(0,8\text{ h})$.The mean $t_{1/2}$ increased from 3.5 to 4.5 h when telaprevir was administered with ketoconazole.

In study 008, PK parameters of telaprevir were determined after either multiple doses of 750 mg telaprevir every 8 h alone or after multiple doses of 1250 mg telaprevir every 8 h plus a single dose of 400 mg ketoconazole. The mean plasma telaprevir concentration vs.time profiles are shown in Figure 2. After multiple doses of 1250 mg telaprevir with a single dose of 400 mg ketoconazole co-administered with the final telaprevir dose, small increases in telaprevir exposure were observed as compared with exposure after multiple 750 mg doses of telaprevir alone: C_{max} increased 1.17-fold and $AUC(0,\infty)$ increased 1.21-fold (Table 2). In comparison with the 750 mg every 8 h dose, the 1250 mg every 8 h dose also resulted in higher mean pre dose concentrations of telaprevir (Figure 2) resulting in parallel profiles.

The calculated mean (SD) PK parameters for a single dose of 400 mg ketoconazole in the presence of co-administered telaprevir in study 003 were 62.5 (18.5) $\mu\text{g h ml}^{-1}$ for $AUC(0,\infty)$ and 6.9 (1.5) $\mu\text{g ml}^{-1}$ for C_{max} , and in study 008 were 44.9 (15.3) $\mu\text{g h ml}^{-1}$ for $AUC(0,8\text{ h})$ and 7.7 (2.6) $\mu\text{g ml}^{-1}$ for C_{max} . These values were similar to those previously reported in the literature [15]. Therefore it could be concluded that adequate exposures of ketoconazole were achieved for the assessment of a CYP3A4 drug interaction.

Figure 1
Mean telaprevir plasma concentration vs. time profiles for telaprevir after single dose administration with or without ketoconazole (study 003). Error bars represent SDs; $n = 17$. $\square$, telaprevir; $\circ$, telaprevir and ketoconazole

Table 2
Effect of ketoconazole on single dose and steady-state PK parameters of telaprevir

Substrate (Day of PK)	Interacting drug	n	C_{max} (ng ml ⁻¹)	$t_{1/2}$ (h)	Arithmetic mean (SD)		GLS mean ratio* (90%CI)		
					AUC (ng ml ⁻¹ h)	C_{min} (ng ml ⁻¹)	C_{max}	AUC	C_{min}
Study 003	None	17	2020 (843)	3.5 (0.5)	12385† (5528)	NA			
	Ketoconazole, 400 mg single dose	17	2430 (786)	4.5 (1.0)	19315† (6970)	NA	1.24 (1.10; 1.41)	1.62 (1.45; 1.81)	NA
Study 008	None	82	3617 (900)		23177‡ (6210)	2207 (710)			
	Ketoconazole, 400 mg with fourth telaprevir dose	81	4274 (859)	ND	27879‡ (5627)	2738 (613)	1.17 (1.12; 1.23)	1.21 (1.16; 1.26)	1.20 (1.13; 1.26)

*Value with telaprevir with interacting drug : value with telaprevir alone. † $AUC(0,\infty)$. ‡ $AUC(0,8\text{ h})$.

Figure 2

Mean telaprevir plasma concentration vs. time profiles for telaprevir after multiple dose administration with or without a single dose of ketoconazole administered with the final dose of telaprevir (study 008). Error bars represent SDs; $n = 82$ for telaprevir alone; $n = 81$ for telaprevir with 400-mg ketoconazole. $\square$, telaprevir 750 mg every 8 h; $\circ$ telaprevir 1250 mg every 8 h and 400 mg ketoconazole

Figure 3

Mean plasma concentration vs. time profile of a single dose of telaprevir following oral administration with and without rifampicin at steady-state (study 016). Error bars represent SDs; $n = 16$. $\bullet$, without rifampicin; $\circ$, with rifampicin

Effect of rifampicin on the pharmacokinetics of telaprevir

The mean plasma concentration vs. time profiles for a single 750 mg dose of telaprevir and efavirenz at steady-state are shown in Figures 3, 4 and 5 and their PK parameters are summarized in Table 3.

When rifampicin was co-administered with telaprevir, telaprevir $AUC(0,\infty)$ was reduced by approximately 92%, telaprevir C_{max} was reduced by approximately 86% and telaprevir $t_{1/2}$ was reduced by approximately 50%.

Table 3

Effect of rifampicin on single dose PK parameters of telaprevir, and the effect of efavirenz on steady-state PK parameters of telaprevir

Substrate (Day of PK)	Inter-acting drug	Volunteers with PK Data (M/F)	C_{max} (ng ml ⁻¹)	$t_{1/2}$ (h)	Arithmetic mean (SD) AUC (ng ml ⁻¹ h)	C_{min} (ng ml ⁻¹)	C_{max}	GLS mean ratio* (90% CI) AUC	C_{min}
Telaprevir 750 mg single dose (D1)	None	13/3	1899 (940)	3.8 (0.8)	10586† (5512)	NA			
Telaprevir 750 mg single dose (D9)	Rifampin 600 mg once daily, D2–9	13/3	249 (106)	2.1 (0.7)	838† (335)	NA	0.14 (0.11, 0.18)	0.08 (0.07, 0.11)	NA*
Telaprevir 750 mg every 8 h, D1–10, D28–37 (D10)	None	25/40	2478 (632)	NA	15275‡ (4303)	1284 (452)			
Telaprevir 750 mg every 8 h, D1–10, D28–37 (D37)	Efavirenz 600 mg once daily, D18–37	21/0	2297 (627)	NA	11523‡ (3663)	745 (352)	0.91 (0.81, 1.02)	0.74 (0.65, 0.84)	0.53 (0.44, 0.65)
Efavirenz 600 mg once daily, D18–37 (D27)	None	21/0	3997 (964)	NA	57118§ (19574)	1642 (656)			
Efavirenz 600 mg once daily, D18–37 (D37)	Telaprevir 750 mg every 8 h, D28–37	21/0	3433 (1019)	NA	53551§ (20035)	1636 (738)	0.84 (0.76, 0.93)	0.93 (0.87, 0.98)	0.98 (0.94, 1.0)

*Value with telaprevir with interacting drug : value with telaprevir alone. †AUC(0,8 h). ‡AUC(0,24 h).

Figure 4

Mean plasma concentration vs. time profile of steady-state telaprevir with and without efavirenz at steady-state (Study 016). Error bars represent SDs; $n = 25$ for without efavirenz and $n = 21$ for with efavirenz. ●, without efavirenz; ○, with efavirenz

The calculated mean (SD) PK parameters for steady state rifampicin (600 mg once daily for 8 days) co-administered with a single dose of telaprevir in study 016 were $52.3 (23.8) \mu\text{g h ml}^{-1}$ for $\text{AUC}(0,24 \text{ h})$ and $12.8(4.6) \mu\text{g ml}^{-1}$ for C_{max} . These values were similar to those previously reported in the literature [16, 17] and, therefore, adequate exposures of rifampicin were achieved for the assessment of a CYP3A4 drug interaction.

Effect of efavirenz on the pharmacokinetics of telaprevir

The mean plasma concentration vs. time profiles for telaprevir at steady-state administered alone or co-administered with efavirenz also at steady-state are shown in Figure 4 and their PK parameters are summarized in Table 3.

When efavirenz was co-administered with telaprevir, telaprevir $\text{AUC}(0,8 \text{ h})$ was reduced by approximately 26%, telaprevir C_{max} was reduced by approximately 9%, and telaprevir C_{min} was reduced by approximately 46%. TCo-administration with telaprevir had no significant effect on efavirenz AUC or minimum observed plasma concentrations (C_{min}), but reduced C_{max} by approximately 16%.

Safety

In all three clinical studies, there were no serious, life-threatening or severe adverse events, and no clinically significant trends noted for any of the clinical laboratory parameters or vital signs.

In study 003, there were no discontinuations due to adverse events. The majority of adverse events were mild in severity. Moderate headaches were reported by two volunteers after dosing with telaprevir and by one volunteer after dosing with telaprevir and ketoconazole. In study 008, two of 89 volunteers discontinued from the study due to

Figure 5

Mean plasma concentration vs. time profile of efavirenz following oral administration with telaprevir and without telaprevir (study 016). Error bars represent SDs; $n = 21$ for without telaprevir and $n = 21$ for with telaprevir. ●, without telaprevir; ○, with telaprevir

adverse events that occurred after telaprevir and/or ketoconazole dosing: one volunteer discontinued due to a mild rash that occurred on the first day of dosing with telaprevir, and another volunteer discontinued due to sinus congestion 2 days following dosing with 400 mg ketoconazole. The majority of adverse events were mild in severity. One volunteer reported moderate vomiting during the telaprevir dosing regimen. Two additional volunteers discontinued due to adverse events (papulosquamous rash and headache) in another arm of this study (moxifloxacin treatment, not further discussed herein).

In study 016, four of 44 volunteers discontinued study drug due to adverse events: moderate intensity rash (during telaprevir dosing regimen), moderate intensity drug reaction rash (during efavirenz dosing regimen), severe dizziness and moderate vomiting (during efavirenz dosing regimen) and moderate agitation and mild visual hallucinations (during efavirenz dosing regimen). Discontinuations were all considered to be related to study drug. The majority of adverse events were mild in severity. In part 1 (rifampicin comparison), 38% ($n = 6$) of the volunteers presented with chromaturia, an event known to be associated with rifampicin use and one volunteer reported moderate headache. In part 2 (efavirenz comparison), 13 (39%) volunteers reported moderate adverse events (dizziness, nausea, vomiting, rash, abdominal pain, agitation, pruritus, epigastric discomfort, altered mood and drug eruption) and a single volunteer reported severe dizziness. The onset of the majority of related/possibly related adverse events occurred on days of efavirenz dosing (36 out of a total of 62 related/possibly related adverse events reported) and on days of efavirenz and telaprevir co-administration (16 out of 62 related/possibly related adverse events reported).

Discussion

Ketoconazole, a potent inhibitor of CYP3A, caused increased exposure of telaprevir in single dose studies. In study 003, a single dose of ketoconazole (400 mg) increased telaprevir AUC approximately 1.6-fold. Generally, multiple doses of ketoconazole 400 mg once daily is recommended to evaluate the effect on a co-administered CYP3A substrate [14]. However, the effect of single dose ketoconazole 400 mg on the exposure to midazolam may provide a close approximation of the effect after multiple doses of ketoconazole 400 mg once daily [18]. After simultaneous intake of ketoconazole and midazolam a 10-fold increase in the exposure to midazolam was observed, compared with a 14-fold increase after 5 days of ketoconazole 400 mg once daily [18]. For these reasons, a significant increase in telaprevir exposure after multiple doses of ketoconazole compared with a single dose is considered to be unlikely. However, it is acknowledged that the increase in single dose telaprevir exposure observed after co-administration of single dose ketoconazole may not reflect the maximal effect of ketoconazole possible on single dose telaprevir PK.

Results in study 008 indicate that the effect of ketoconazole on telaprevir exposure is diminished after multiple doses of telaprevir. Specifically, despite a 1.7-fold higher dose of telaprevir (an increase from 750 mg every 8 h to 1250 mg every 8 h), and the co-administration of 400 mg ketoconazole, the exposure of telaprevir increased only approximately 1.2-fold. Since the pre dose concentrations of telaprevir (before the ketoconazole dose was administered) were also higher (increased in parallel) after the 1250 mg every 8 h dose compared with the 750 mg every 8 h dose, the increased concentrations can be attributed to the increased dose rather than an effect of ketoconazole. This observation suggests that the effect of ketoconazole on telaprevir exposure at steady-state is minimal, if any, and less than that after a single dose of telaprevir. The limited effect of CYP3A inhibition by ketoconazole on telaprevir exposure is likely due to the strong inhibition of CYP3A by telaprevir itself [19].

It is possible that with the usual dose of telaprevir (750 mg every 8 h), the effect of ketoconazole may have been more than that observed here. However, a similar lack of effect of ketoconazole was observed on other CYP3A substrates that were also strong inhibitors of CYP3A, such as atazanavir [20] and lopinavir [21] when multiple doses of atazanavir or lopinavir/ritonavir were administered.

Similar results were obtained in another clinical study, in which telaprevir and the CYP3A inhibitor ritonavir were co administered, that showed increased telaprevir exposure after a single dose of telaprevir with ritonavir, but no increase in telaprevir exposure on co administration of ritonavir when both were at steady-state [22]. In that study in healthy volunteers, a single dose of ritonavir (100 mg) increased telaprevir AUC after a single dose of 750 mg telaprevir

approximately 2-fold. However, co-administration of 750 mg telaprevir every 12 h with low dose (100 mg) ritonavir every 12 h for 14 days resulted in 15% to 32% lower telaprevir exposure when both drugs were at steady-state on day 14 as compared with multiple dosing with 750 mg telaprevir every 8 h alone, suggesting no significant effect of ritonavir on telaprevir metabolism at steady-state. The ratio of telaprevir AUC on day 14 : day 1 was 2.52 in the telaprevir 750 mg every 8 h group compared with 0.85 in the telaprevir/ritonavir (750 mg/100 mg every 12 h) group. While these results may be possibly due to the dual (inhibitory and inductive) nature of ritonavir [23], the lack of significant boosting was observed as early as the second day of co-administration when induction was unlikely to have an effect. After multiple doses of telaprevir, due to the inhibition of the CYP3A pathway by telaprevir itself, the non-CYP mediated metabolic pathways (amide hydrolysis and reduction) are likely to be the dominant pathway for telaprevir metabolism while CYP3A activity is largely suppressed by telaprevir. Therefore, at steady-state, drug interactions with CYP3A inhibitors are unlikely to increase telaprevir exposure greatly.

The strong CYP3A inducer rifampicin markedly reduced exposure to telaprevir. Previous clinical studies have reported that rifampicin enhanced metabolism of other drugs that are substrates of CYP3A, necessitating increased dosages of these drugs or use of alternative compounds to maintain adequate clinical responses when these medications are co-administered with rifampicin [24]. The effect of rifampicin on the PK of telaprevir is consistent with these reports. However, the effect of rifampicin after steady-state dosing of telaprevir (where the CYP3A inhibition by telaprevir may oppose the inducing effect of rifampicin) is not known.

Co-administration of efavirenz with telaprevir at steady-state led to a decrease in telaprevir C_{min} of approximately 46% and AUC by 26%, whereas the C_{max} of telaprevir was unaffected. These results are consistent with a moderate effect on inducing CYP3A activity by efavirenz. Co-administration of telaprevir did not affect the steady-state AUC or C_{min} of efavirenz, and the average C_{max} of efavirenz was reduced by approximately 16%. Although a value for the minimum C_{min} that would be required for efficacy has not been established, it was considered desirable to achieve closer to the C_{min} values that were obtained in phase 3 studies that demonstrated efficacy for telaprevir. Therefore, based on the results presented here, a study in healthy volunteers that examined the effect of a combination of tenofovir disoproxil fumarate (300 mg once daily) and efavirenz (600 mg once daily) on telaprevir given at a higher dose of 1125 mg every 8 h or 1500 mg twice daily was conducted. The results indicated that the increased dose of 1125 mg every 8 h regimen of telaprevir could partly offset the effect of efavirenz on telaprevir PK [25]. An ongoing pilot study of telaprevir in HIV/HCV co-infected patients is being conducted with a dose of telaprevir of

1125 mg every 8 h when given in combination with efavirenz-containing regimens of antiretrovirals [26].

In general, all regimens were well-tolerated in the healthy volunteers in these studies. In study 016, it should be mentioned that efavirenz was administered in the morning so that intense PK sampling could be accomplished while the volunteer was scheduled to remain awake, which differs from the usual evening administration (at bedtime) that is recommended because of the dizziness, impaired concentration and/or drowsiness that can be associated with efavirenz use [27]. Most common symptoms reported in the efavirenz package insert include dizziness (28.1%), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%) and hallucinations (1.2%). Efavirenz and telaprevir treatment was considered to be well-tolerated in study 016. There were no serious adverse events and only four volunteers discontinued due to adverse events but it is possible that had efavirenz been dosed in the evening that volunteers may have better tolerated some of the events that led to discontinuation (e.g. one report of severe dizziness and moderate vomiting, one report of moderate agitation and mild visual hallucinations) as well as the other events that did not lead to discontinuation (e.g. 14 [50%] volunteers reported adverse events of dizziness). However, a study in 49 HIV-infected patients suggested that morning dosing of efavirenz may be well tolerated and lead to better adherence [28].

In conclusion, ketoconazole (and possibly other CYP3A inhibitors) are likely to result in increased telaprevir exposure initially. However after repeat dosing of telaprevir, the effect is likely to be reduced. Telaprevir can also increase the exposure of ketoconazole. Therefore, high doses of ketoconazole and itraconazole (>200 mg day⁻¹) are not recommended [8–11]. Although telaprevir exposure was significantly reduced by the potent CYP3A inducer rifampicin, it was less affected by the moderate inducer efavirenz.

Competing Interests

This study was supported by Vertex Pharmaceuticals Incorporated (Vertex) and Tibotec BVBA (Tibotec). VG, GC, YY, NA, LM, KA and FS were employees and/or stock owners of Vertex at the time this work was performed. RvH is an employee of Janssen Infectious Diseases BVBA (formerly Tibotec BVBA) and a stock owner of Johnson and Johnson.

The authors acknowledge the contribution of Alan S. Marion, MD, PhD, MDS Pharma Services, 621 Rose Street, Lincoln, NE 68502, Thomas L. Hunt, MD, PhD, PPD Development, 7551 Metro Center Drive, Suite 200, Austin, TX, USA 78744 and Adel Nada, MD, MS, Charles River Clinical Services–Northwest Kinetics, 3615 Pacific Avenue, Tacoma, WA 98418 who were contracted to serve as investigators on Studies 003, 008, and 016, respectively. The authors acknowledge the contribution of Lakshmi Viswanathan for help in the preparation

of this manuscript, Kristin Stephan, PhD and Susan Wu, PhD, provided manuscript and editorial coordination support and Jonathan Kirk provided graphical design support. All are employees and stockholders of Vertex Pharmaceuticals Incorporated.

REFERENCES

- 1 Lin C, Kwong AD, Perni RB. Discovery and development of VX-950, a novel, covalent, and reversible inhibitor of hepatitis C virus NS3.4A serine protease. *Infect Disord Drug Targets* 2006; 6: 3–16.
- 2 McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, McNair L, Alam J, PROVE1 Study Team. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009; 360: 1827–38. [erratum: *N Engl J Med* 2009; 361: 1516.].
- 3 Hézode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, Bronowicki JP, Bourlière M, Gharakhanian S, Bengtsson L, McNair L, George S, Kieffer T, Kwong A, Kauffman RS, Alam J, Pawlotsky JM, Zeuzem S, PROVE2 Study Team. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009; 360: 1839–50.
- 4 McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, Heathcote EJ, Zeuzem S, Reesink HW, Garg J, Bsharat M, George S, Kauffman RS, Adda N, Di Bisceglie AM, PROVE3 Study Team. Telaprevir for previously treated chronic HCV infection. *N Engl J Med* 2010; 362: 1292–303. [erratum: *N Engl J Med* 2010; 362: 1647.].
- 5 Jacobson IM, McHutchison JG, Dusheiko GM, Di Bisceglie AM, Reddy KR, Bzowej NH, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS, Zeuzem S, ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; 364: 2405–16.
- 6 Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, Ferenci P, Nevens F, Müllhaupt B, Pockros P, Terg R, Shouval D, van Hoek B, Weiland O, Van Heeswijk R, De Meyer S, Luo D, Boogaerts G, Polo R, Picchio G, Beumont M, REALIZE Study Team. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; 364: 2417–28.
- 7 Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, Fried MW, Adler M, Reesink HW, Martin M, Sankoh AJ, Adda N, Kauffman RS, George S, Wright CI, Poordad, ILLUMINATE Study Team. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011; 365: 1014–24. [Erratum: *N Engl J Med* 2011; 365: 1551].
- 8 INCIVEK [US prescribing information]. Cambridge, MA: Vertex Pharmaceuticals Incorporated; 2012. Available at http://pi.vrtx.com/files/uspi_telaprevir.pdf (last accessed 29 June 2012).

- 9 INCIVEK [Canada product monograph]. Laval, Quebec, Canada: Vertex Pharmaceuticals Incorporated; 2011. Available at http://pi.vrtx.com/files/canadapm_telaprevir_en.pdf (last accessed 29 June 2012).
- 10 INCIVO [EU summary of product characteristics]. Beerse, Belgium: Janssen Cilag NV; 2012. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002313/WC500115529.pdf (last accessed 29 June 2012).
- 11 TELAVIC [package insert]. Osaka, Japan: Mitsubishi Tanabe Pharma; 2011.
- 12 US Department of Health and Human Services. Guidance for industry: bioanalytical assay validation. 2001; Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf> (last accessed 29 June 2012).
- 13 Garg V, van Heeswijk R, Yang Y, Kauffman R, Smith F, Adda N. The pharmacokinetic interaction between an oral contraceptive containing ethinyl estradiol and norethindrone and the HCV protease inhibitor telaprevir. *J Clin Pharmacol* 2012; e-pub ahead of print, DOI: 10.1177/0091270011419855.
- 14 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling. September 2006.
- 15 Daneshmend TK, Warnock DW, Ene MD, Johnson EM, Potten MR, Richardson MD, Williamson PJ. Influence of food on the pharmacokinetics of ketoconazole. *Antimicrob Agents Chemother* 1984; 25: 1–3.
- 16 Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivistö KT. Pharmacokinetic interaction with rifampin: clinical relevance. *Clin Pharmacokinet* 2003; 42: 819–50.
- 17 Rifampin Capsules [US prescribing information]. Marietta, Georgia: VersaPharm Incorporated; 2003. Available at <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=26a2dbca-5090-4f6c-99ed-e11a70bb5af0> (last accessed 29 June 2012).
- 18 Stoch SA, Friedman E, Maes A, Yee K, Xu Y, Larson P, Fitzgerald M, Chodakewitz J, Wagner JA. Effect of different durations of ketoconazole dosing on the single-dose pharmacokinetics of midazolam: Shortening the paradigm. *J Clin Pharmacol* 2009; 49: 398–406.
- 19 Garg V, Chandorkar G, Farmer F, Smith F, Alves K, van Heeswijk RPG. The effect of telaprevir on the pharmacokinetics of midazolam and digoxin. *J Clin Pharmacol* 2012; e-pub ahead of print, DOI: 10.1177/0091270011419850.
- 20 REYATAZ. [US prescribing information]. 2011. Princeton, NJ: Bristol-Myers Squibb. Available at http://packageinserts.bms.com/pi/pi_reyataz.pdf (last accessed 29 June 2012).
- 21 KALETRA. [US prescribing information]. 2011. North Chicago, IL: Abbott Laboratories. Available at <http://www.rxabbott.com/pdf/kaletratabpi.pdf> (last accessed 29 June 2012).
- 22 Garg V, Luo X, McNair L, van Heeswijk R, Kauffman R. Low-dose ritonavir and the pharmacokinetics of the investigational HCV protease inhibitor telaprevir in healthy volunteers. Poster presented at: 18th Conference on Retroviruses and Opportunistic Infections; February 2011; Boston, MA. Abstract 629. Available at <http://www.retroconference.org/2011/Abstracts/40192.htm> (last accessed 29 June 2012).
- 23 NORVIR [US prescribing information]. 2012. North Chicago, IL: Abbot Laboratories. Available at <http://www.rxabbott.com/pdf/norpi2a.pdf> (last accessed 29 June 2012).
- 24 Venkatesan K. Pharmacokinetic drug interactions with rifampicin. *Clin Pharmacokinet* 1992; 22: 47–65.
- 25 van Heeswijk R, Vandevoorde A, Boogaerts G, Vangeneugden T, de Paepe E, Polo R, van Solingen-Ristea R, de Backer K, Garg V, Beumont M. Pharmacokinetic interactions between antiretroviral agents and the investigational HCV protease inhibitor telaprevir in healthy volunteers. Oral presentation at: 18th Conference on Retroviruses and Opportunistic Infections; February 2011; Boston, MA. Abstract 119.
- 26 Sulkowski M, Dieterich D, Sherman K, Rockstroh JK, Adda N, Mahnke L, Garg V, Charakhanian S, McCallister S, Soriano V. Interim analysis of a phase 2a double-blind study of telaprevir in combination with pegylated interferon- α 2a and ribavirin in HIV/HCV co-infected patients. Oral presentation at: 18th Conference on Retroviruses and Opportunistic Infections; February 2011; Boston, MA. Abstract 146LB. Available at <http://www.retroconference.org/2011/Abstracts/42467.htm> (last accessed 29 June 2012).
- 27 SUSTIVA [US prescribing information]. 2011. Princeton, New Jersey: Bristol-Myers Squibb. Available at http://packageinserts.bms.com/pi/pi_sustiva.pdf (last accessed 29 June 2012).
- 28 Skeie L, Maeland A. Can efavirenz be taken in the morning? *Scan J Infect Dis* 2006; 38: 1089–91.