MAJOR ARTICLE

Clinical Assessment of Potential Drug Interactions of Faldaprevir, a Hepatitis C Virus Protease Inhibitor, With Darunavir/Ritonavir, Efavirenz, and Tenofovir

John P. Sabo,[1] Jens Kort,[1] Charles Ballow,[2] Manuel Haschke,[3] Manuel Battegay,[3] Rainard Fuhr,[4] Birgit Girlich,[5] Michael Schobelock,[1] Ulrich Feifel,[6] Benjamin Lang,[7] Yongmei Li,[1] and Mabrouk Elgadi[8]

[1]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, Connecticut; [2]Buffalo Clinical Research Center, New York; [3]University Hospital Basel, Switzerland; [4]PAREXEL International GmbH, Berlin, Germany; [5]Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland; [6]Boehringer Ingelheim Pharma GmbH and Co KG, Ingelheim, and [7]Boehringer Ingelheim Pharma GmbH and Co KG, Biberach, Germany; and [8]Boehringer Ingelheim Ltd, Burlington, Ontario, Canada

Background. Faldaprevir is a potent, once-daily hepatitis C virus (HCV) NS3/4A protease inhibitor. Studies were performed to investigate potential drug interactions between faldaprevir and the commonly used antiretrovirals darunavir/ritonavir, efavirenz, and tenofovir to guide the coadministration of faldaprevir with these agents in human immunodeficiency virus/HCV–coinfected patients.

Methods. In 3 open-label, phase 1 pharmacokinetic (PK) studies, healthy adult volunteers received (1) darunavir/ritonavir (800 mg/100 mg once daily) with and without faldaprevir (240 mg once daily); (2) faldaprevir (240 mg twice daily) with and without efavirenz (600 mg once daily); or (3) faldaprevir (240 mg twice daily) or tenofovir (300 mg once daily) alone and in combination. To assess potential drug interactions, geometric mean ratios and 90% confidence intervals for PK parameters were calculated. Safety was evaluated.

Results. Efavirenz decreased faldaprevir area under the concentration-time curve (AUC) by 35%, C_{max} by 28%, and C_{min} by 46%, consistent with induction of CYP3A by efavirenz. Tenofovir decreased faldaprevir AUC by 22%, which was not considered to be clinically relevant. Faldaprevir had no clinically relevant effects on darunavir or tenofovir PK (15% and 22% AUC increase, respectively). Adverse events were consistent with the known safety profiles of faldaprevir and the antiretrovirals being examined.

Conclusions. No clinically significant interactions were observed between faldaprevir and darunavir/ritonavir or tenofovir. A potentially clinically relevant decrease in faldaprevir exposure was observed when coadministered with efavirenz; this decrease can be managed using the higher of the 2 faldaprevir doses tested in phase 3 trials (240 mg once daily as opposed to 120 mg once daily).

Keywords. antiretrovirals; drug–drug interactions; faldaprevir; HCV; HIV.

Faldaprevir (BI 201335) is a selective novel hepatitis C virus (HCV) NS3/4A protease inhibitor that has shown potent in vitro inhibition of HCV genotypes 1, 4, 5, and 6 [1]. Unlike the protease inhibitors boceprevir and telaprevir, which are administered 2–3 times daily, the long elimination half-life of faldaprevir (20–30 hours) allows oral once-daily administration [2]. Faldaprevir, in combination with pegylated interferon-α (peg-IFN) and ribavirin (RBV), has been investigated in phase 3 clinical trials in HCV genotype 1–infected patients at doses of 120 and 240 mg once daily. The STARTVerso1 trial in treatment-naive patients showed that faldaprevir plus peg-IFN and RBV was effective and well tolerated, and achieved sustained virologic response rates of 79%

Received 12 December 2013; accepted 25 July 2014; electronically published 4 August 2014.

Correspondence: John P. Sabo, MS, Boehringer Ingelheim Pharmaceuticals, Inc, 900 Ridgebury Rd, Ridgefield, CT 06877 (john.sabo@boehringer-ingelheim.com).

Clinical Infectious Diseases® 2014;59(10):1420–8

DOI: 10.1093/cid/ciu616

(120 mg once daily) and 80% (240 mg once daily) at 12 weeks following treatment, compared with 52% in patients who received placebo plus peg-IFN and RBV ($P < .0001$) [3]. In addition, the STARTVerso4 trial investigated faldaprevir (120 and 240 mg once daily) in combination with peg-IFN/RBV in 308 treatment-naive or previously relapsed patients coinfected with human immunodeficiency virus (HIV) and HCV [4]. Preliminary data from this trial have demonstrated high sustained virologic response rates with faldaprevir treatment (HCV RNA undetectable 4 weeks after completing therapy): 79% and 84% in patients treated with 240 mg once daily for 12 and 24 weeks, respectively, and 72% in patients treated with 120 mg once daily for 24 weeks [4].

HIV coinfection accelerates HCV disease progression and increases the risk of advanced fibrosis, cirrhosis, and hepatocellular carcinoma [5–8]. As such, coinfected individuals have an urgency for HCV treatment. Treatment guidelines recommend that in HIV/HCV-coinfected patients receiving combination antiretroviral (ARV) therapy (cART), HCV treatment should be administered where feasible [9–11], and should be initiated when HIV replication is controlled [11]. Therefore, there is a great need for effective HCV treatments that have a low potential for drug–drug interactions with ARVs and can be coadministered safely with most or all contemporary cART regimens. Faldaprevir at steady state after 240 mg twice-daily dosing is a weak inhibitor of cytochrome P450 (CYP) 2C9 and a moderate inhibitor of CYP3A [12], and in vitro studies have shown that faldaprevir is a CYP3A substrate [13].

Here we describe the results from 3 phase 1 pharmacokinetic (PK) studies with faldaprevir conducted in healthy volunteers. The primary objective was to investigate the potential drug interactions with darunavir/ritonavir, efavirenz, and tenofovir to guide the safe coadministration of faldaprevir and these antiretrovirals in HIV/HCV genotype 1–coinfected patients.

METHODS

Study Drugs

In separate studies, recommended clinical doses of darunavir/ritonavir (800 mg/100 mg once daily), efavirenz (600 mg once daily), or tenofovir disoproxil fumarate (300 mg once daily) were administered to healthy volunteers. Faldaprevir daily doses were 240 mg once daily in the darunavir/ritonavir study and 240 mg twice daily in the efavirenz and tenofovir studies. The faldaprevir 240 mg twice-daily dosing used in the efavirenz and tenofovir studies in healthy volunteers was chosen to provide exposure comparable to that observed with faldaprevir 240 mg once daily in HCV-infected patients, which is the highest dose being investigated in phase 3 trials [14]. In all studies, faldaprevir loading doses were used for the first dose (see below), similar to the loading dose schedule used in patients with HCV.

Study Designs

Three open-label phase 1 PK studies were conducted in healthy adult volunteers (Figure 1). Healthy male and female volunteers aged 18–55 years with a body mass index of 18.5–29.9 kg/m^2 were enrolled. All studies were approved by the responsible institutional review board and were carried out in compliance with the Declaration of Helsinki, in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and applicable regulatory requirements. Each participant provided written informed consent prior to initiation of study procedures.

Darunavir/Ritonavir Study

To assess the effects of faldaprevir on the PK of darunavir when coadministered with ritonavir, subjects received faldaprevir on days 9–16 and darunavir plus ritonavir on days 1–16. Faldaprevir was given as a loading dose (480 mg) on day 9 followed by 240 mg once daily thereafter. Ritonavir is a CYP3A inhibitor that increases exposure of coadministered HIV protease inhibitors metabolized by CYP3A [15]. In vitro studies have shown that faldaprevir is a CYP3A substrate [13]. A dose of faldaprevir 240 mg once daily was selected for this study population because of the expected increase in faldaprevir exposure in the presence of ritonavir.

Efavirenz Study

To assess the effects of efavirenz (a moderate CYP3A inducer [16]) on the PK of faldaprevir, subjects received faldaprevir on days 2–18 and efavirenz 600 mg once daily on days 10–18 (Figure 1). Faldaprevir was given as a loading dose (480 mg initially then 240 mg 12 hours later) when first administered (day 2), followed by 240 mg twice daily thereafter. To assess the effect of faldaprevir and combined effects of faldaprevir and efavirenz on CYP3A metabolism, oral midazolam 7.5 mg once daily was administered as a probe substrate on days 1, 9, and 18.

Tenofovir Study

To assess the effects of faldaprevir on the PK of tenofovir and vice versa, subjects received faldaprevir on days 8–22 and tenofovir 300 mg once daily on days 1–15. Faldaprevir was given as a loading dose on day 8 (480 mg initially then 240 mg 12 hours later), followed by 240 mg twice daily until day 21, and 240 mg administered in the morning only on day 22.

Pharmacokinetic Evaluation

Blood samples were collected at predetermined time points (Figure 1). Plasma concentrations of drugs of interest were determined by commercially available liquid chromatography–tandem mass spectrometry methods (Tandem Laboratories, Salt Lake City, Utah). The lower limits of quantification for the study medications were faldaprevir 2 ng/mL; darunavir 25 ng/mL; midazolam and 1-hydroxymidazolam 0.2 ng/mL; and tenofovir 1 ng/mL.

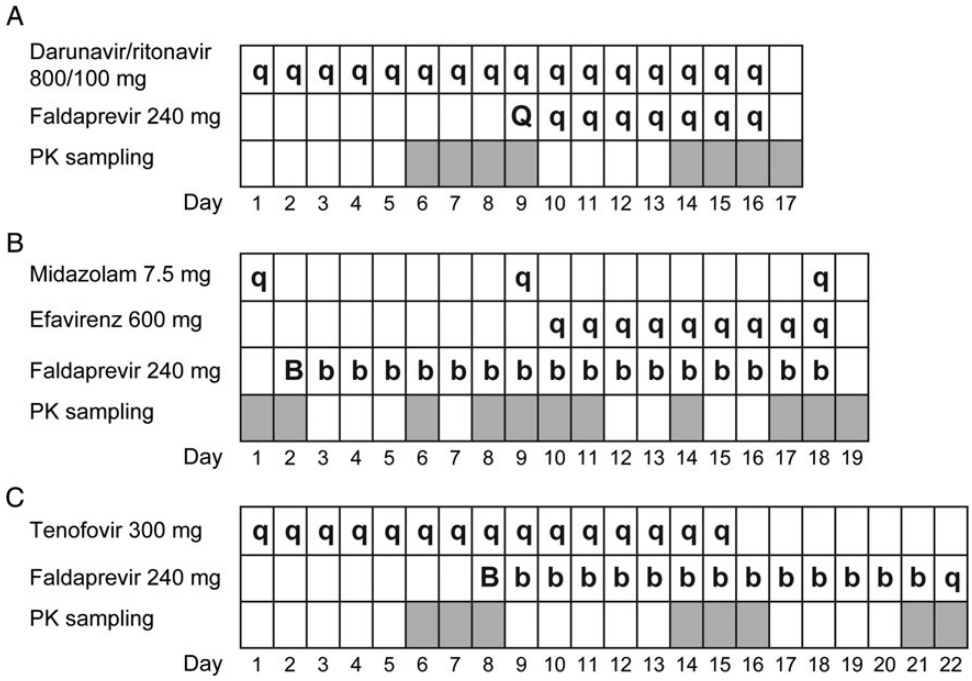

Figure 1. Study designs and pharmacokinetic (PK) sampling schedule for the darunavir/ritonavir (*A*), efavirenz (*B*), and tenofovir (*C*) studies. Shaded boxes indicate PK sampling days. Abbreviations: b, twice daily; B, faldaprevir loading dose within twice-daily schedule (480 mg followed by 240 mg 12 hours later); q, once daily/single dose; Q, faldaprevir loading dose within once-daily schedule (480 mg).

Samples containing analyte and internal standard were extracted and analyzed in an API 3000 (darunavir), API 4000 (faldaprevir), or API 5000 (midazolam/1-hydroxymidazolam and tenofovir) mass spectrometer (AB SCIEX, Framingham, Massachusetts). Quantitation was determined using linear (faldaprevir, midazolam/1-hydroxymidazolam, and tenofovir) or quadratic (darunavir) weighted regression analysis ($1/x^2$) of peak area ratios of analytes and internal standards. Calibration standards were placed at the beginning and end of each bioanalytical run. The calibration curves were linear, and ranges were faldaprevir 2–2000 ng/mL; darunavir 25–12 500 ng/mL; midazolam and 1-hydroxymidazolam 0.2–10 ng/mL; and tenofovir 1–500 ng/mL. Assay performance during the study was assessed by back-calculation of calibration standards, assessment of the standard curve fit, and comparison with quality control samples of blank human plasma. Adequate accuracy and precision of the assay were observed when compared with quality control samples.

Statistical Analysis

Steady-state PK parameters, including area under the plasma concentration-time curve (AUC), minimum plasma concentration (C_{min}), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and oral clearance (CL/F) were calculated using noncompartmental PK analysis (Pharsight WinNonlin version 5.3, Mountain View, California). To assess potential drug interactions, adjusted geometric mean ratios (GMRs) and 2-sided 90% confidence intervals (CIs) for AUC, C_{max}, and C_{min} were calculated using SAS version 9.2 (Cary, North Carolina).

Safety Evaluation

Safety was assessed by physical examination, monitoring of vital signs, laboratory tests, 12-lead electrocardiography (ECG), and adverse events (AEs) at prespecified time-points during the study. ECGs were assessed at screening, at end of study visit, and as medically necessary based on investigator judgment. AEs were monitored at screening, every day during treatment, and at the end of study visit. Subjects were also required to report AEs spontaneously, including time of onset, duration, and intensity. AE intensity was graded as mild (awareness of a sign or symptom, which was easily tolerated), moderate (discomfort enough to cause interference with usual activity), or severe (incapacitating or causing inability to work or to perform usual activities). The relationship between study treatment and AEs was assessed by the investigator.

RESULTS

Subjects

Forty-five healthy volunteers received study treatment: 14 in the darunavir/ritonavir study, 15 in the efavirenz study, and 16 in the tenofovir study. Most subjects were male (76% overall; range, 60%–86% across the 3 studies; Table 1). Baseline

Table 1. Subject Baseline Characteristics

Characteristic	Darunavir/ Ritonavir Study	Efavirenz Study	Tenofovir Study
Subjects, No.	14	15	16
Male sex, No. (%)	12 (85.7)	9 (60.0)	13 (81.3)
Age, y, median (range)	42.0 (20–55)	31 (20–53)	37 (25–54)
BMI, kg/m^2, median (range)	22.9 (19.3–29.3)	22.6 (19.1–30.6)	26.6 (20.2–29.7)
Race, %			
White	100	100	50.0
Black	. . .	. . .	50.0

Abbreviation: BMI, body mass index.

characteristics were similar between study groups except for race (50% white, 50% black in the tenofovir study, and 100% white in other studies; Table 1). Four subjects discontinued treatment because of AEs (2 in the efavirenz study and 2 in the tenofovir study). All other subjects completed the studies.

Pharmacokinetics

Steady-state PK parameters for faldaprevir and coadministered drugs are shown in Tables 2 and 3, respectively; adjusted GMRs and 90% CIs for AUC, C_{max}, and C_{min} are shown in Figure 2*A* and 2*B*.

Darunavir/Ritonavir Study

With faldaprevir at steady state, darunavir AUC increased by approximately 15%, C_{max} increased by 28%, and C_{min} decreased by 12% (Table 3; Figure 2*B*). These changes were not considered to be clinically relevant.

Efavirenz Study

Faldaprevir steady-state exposure was lower when coadministered with efavirenz compared with faldaprevir alone, with an approximate 35% decrease in AUC, 28% decrease in C_{max}, and 46% decrease in C_{min} (Table 2; Figure 2*A*). Furthermore, as would be expected following induction of CYP3A by efavirenz, faldaprevir CL/F was higher when faldaprevir was coadministered with efavirenz (Table 2).

Midazolam AUC after a single dose increased by approximately 124% when coadministered with faldaprevir alone (consistent with moderate inhibition of CYP3A by faldaprevir), and decreased by approximately 61% when coadministered with

Table 2. Steady-State Pharmacokinetic Parameters for Faldaprevir, With and Without Coadministered Drug

Parameter	Geometric Mean (Geometric CV%) of Faldaprevir	
		240 mg QD Faldaprevir + 800 mg QD Darunavir +100 mg QD Ritonavir (n = 14)
$AUC_{\tau,ss}$, ng × h/mL		115 000 (58.3)
$C_{max,ss}$, ng/mL		8780 (51.4)
$T_{max,ss}$, h		2.6 (35.3)
$C_{min,ss}$, ng/mL		2660 (78.5)
$CL/F_{,ss}$, mL/min		34.9 (58.3)
	240 mg BID Faldaprevir[a] (n = 15)	240 mg BID Faldaprevir[a] + 600 mg QD Efavirenz (n = 14)[b]
$AUC_{0–12,ss}$, ng × h/mL	225 000 (91.1)	146 000 (148)
$C_{max,ss}$, ng/mL	24 000 (76.4)	17 200 (111)
$T_{max,ss}$, h[c]	3.0 (0.0–4.2)	2.0 (1.0–4.0)
$C_{min,ss}$, ng/mL	14 700 (119)	7650 (277)[c]
$CL/F_{,ss}$, mL/min	17.8 (91.1)	27.5 (148)
	240 mg BID Faldaprevir (n = 14)	240 mg BID Faldaprevir + 300 mg QD Tenofovir (n = 16)
$AUC_{0–12,ss}$, ng × h/mL	523 000 (101)	418 000 (69.3)
$C_{max,ss}$, ng/mL	50 400 (91.3)	41 700 (51.4)
$T_{max,ss}$, h[c]	3.5 (1.5–8.0)	4.0 (2.0–8.0)
$C_{min,ss}$, ng/mL	40 000 (113)	31 000 (79.5)
$CL/F_{,ss}$, mL/min	7.7 (101)	9.6 (69.3)

Abbreviations: AUC, area under the concentration-time curve; AUC_{τ}, area under the concentration–time curve of the analyte in plasma at steady state over a uniform dosing interval τ; BID, twice daily; CL/F, oral clearance; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CV%, percent coefficient of variation; QD, once daily; ss, steady state; T_{max}, time to maximum plasma concentration.

[a] A single dose of midazolam (7.5 mg) was also coadministered.

[b] n = 13 for C_{min}.

[c] Median and range.

Table 3. Pharmacokinetic Parameters for Darunavir, Midazolam, and Tenofovir, With and Without Coadministered Faldaprevir

Parameter	Geometric Mean (Geometric CV%) of Coadministered Drug		
	800 mg QD Darunavir + 100 mg QD Ritonavir (n = 14)	240 mg QD Faldaprevir[a] + 800 mg QD Darunavir + 100 mg QD Ritonavir (n = 14)	
$AUC_{\tau,ss}$, ng × h/mL	57 200 (29.5)	66 000 (39.9)	
$C_{max,ss}$, ng/mL	4930 (23.9)	6330 (26.5)	
$T_{max,ss}$, h	1.7 (33.9)	2.1 (37.3)	
$C_{min,ss}$, ng/mL	1330 (49.5)	1170 (90.3)	
$CL/F_{,ss}$, L/h	14.0 (29.5)	12.1 (39.9)	
	Midazolam[a] (n = 15)	240 mg BID Faldaprevir + Midazolam[a] (n = 15)	240 mg BID Faldaprevir + Midazolam[a] + 600 mg QD Efavirenz (n = 14)
$AUC_{0-\infty}$, nmol × h/L	278 (28.3)	624 (54.3)	110 (88.1)
C_{max}, nmol/L	110 (45.6)	121 (46.1)	44.9 (101)
T_{max}, h[b]	1.0 (0.5–1.5)	1.0 (0.5–3.0)	0.7 (0.5–3.0)
C_{min}, ng/mL	1.4 (49.1)	3.3 (124)	1.3 (53.2)
CL/F, L/h	82.9 (28.3)	37.0 (54.3)	209 (88.1)
	300 mg QD Tenofovir (n = 16)	240 mg BID Faldaprevir + 300 mg QD Tenofovir (n = 16)	
$AUC_{0-24,ss}$, ng × h/mL	2700 (26.5)	3290 (19.6)	
$C_{max,ss}$, ng/mL	300 (27.3)	284 (16.6)	
$T_{max,ss}$, h[b]	2.0 (0.5–4.0)	2.0 (0.5–3.0)	
$C_{min,ss}$, ng/mL	54.0 (26.7)	79.4 (21.5)	
$CL/F_{,ss}$, mL/min	1850 (26.5)	1520 (19.6)	

Abbreviations: AUC, area under the concentration-time curve; AUC_{τ}, area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ; BID, twice daily; CL/F, oral clearance; C_{max}, maximum plasma concentration; C_{min}, minimum plasma; CV%, percent coefficient of variation; QD, once daily; ss, steady state; T_{max}, time to maximum plasma concentration.

[a] Single oral administration of 7.5 mg midazolam.

[b] Median and range.

both faldaprevir and efavirenz, indicating a net induction of CYP3A activity by the combination (Table 3; Figure 2*B*). Trends in AUC for the primary metabolite 1-hydroxymidazolam corresponded with inhibition of CYP3A at the earlier phase and induction of CYP3A at the late phase (data not shown).

Tenofovir Study

Tenofovir had a small effect on steady-state faldaprevir exposure (approximate 22% decrease in AUC, 18% decrease in C_{max}, and 25% decrease in C_{min}; Table 2; Figure 2*A*), which was not considered clinically relevant. Similarly, faldaprevir effects on the steady-state PK of tenofovir (approximate 22% increase in AUC, 5% decrease in C_{max}, and 47% increase in C_{min}; Table 3; Figure 2*B*) were not considered clinically relevant given the relative safety of tenofovir and are consistent with the PK of tenofovir when coadministered with other protease inhibitors [17].

Safety

Across all studies, AEs were mild or moderate in intensity (Table 4), and all AEs resolved within the follow-up period. AEs were consistent with the known safety profiles of faldaprevir and the ARVs being examined. In all studies, no severe AEs were reported and no deaths occurred.

In the darunavir/ritonavir study, treatment-related AEs occurred in 6 subjects (43%) during treatment with darunavir/ritonavir and 11 subjects (79%) during treatment with darunavir/ritonavir plus faldaprevir. In the efavirenz study, all subjects had at least 1 treatment-related AE, and in the tenofovir study, treatment-related AEs were reported in 15 subjects (94%) when faldaprevir and tenofovir were coadministered and in 9 subjects (56%) during treatment with faldaprevir alone. Gastrointestinal and nervous system disorders were the most commonly reported across all studies (Table 4). Rash was reported in 7 subjects (47%) who received efavirenz and faldaprevir, compared with 1 subject (6%) who received tenofovir and faldaprevir; no subjects on darunavir/ritonavir and faldaprevir reported skin-related events. Jaundice was seen in 6 (40%) and 5 subjects (31%) in the efavirenz and tenofovir studies, respectively. Hepatobiliary disorders were not observed in subjects who received darunavir/ritonavir and faldaprevir.

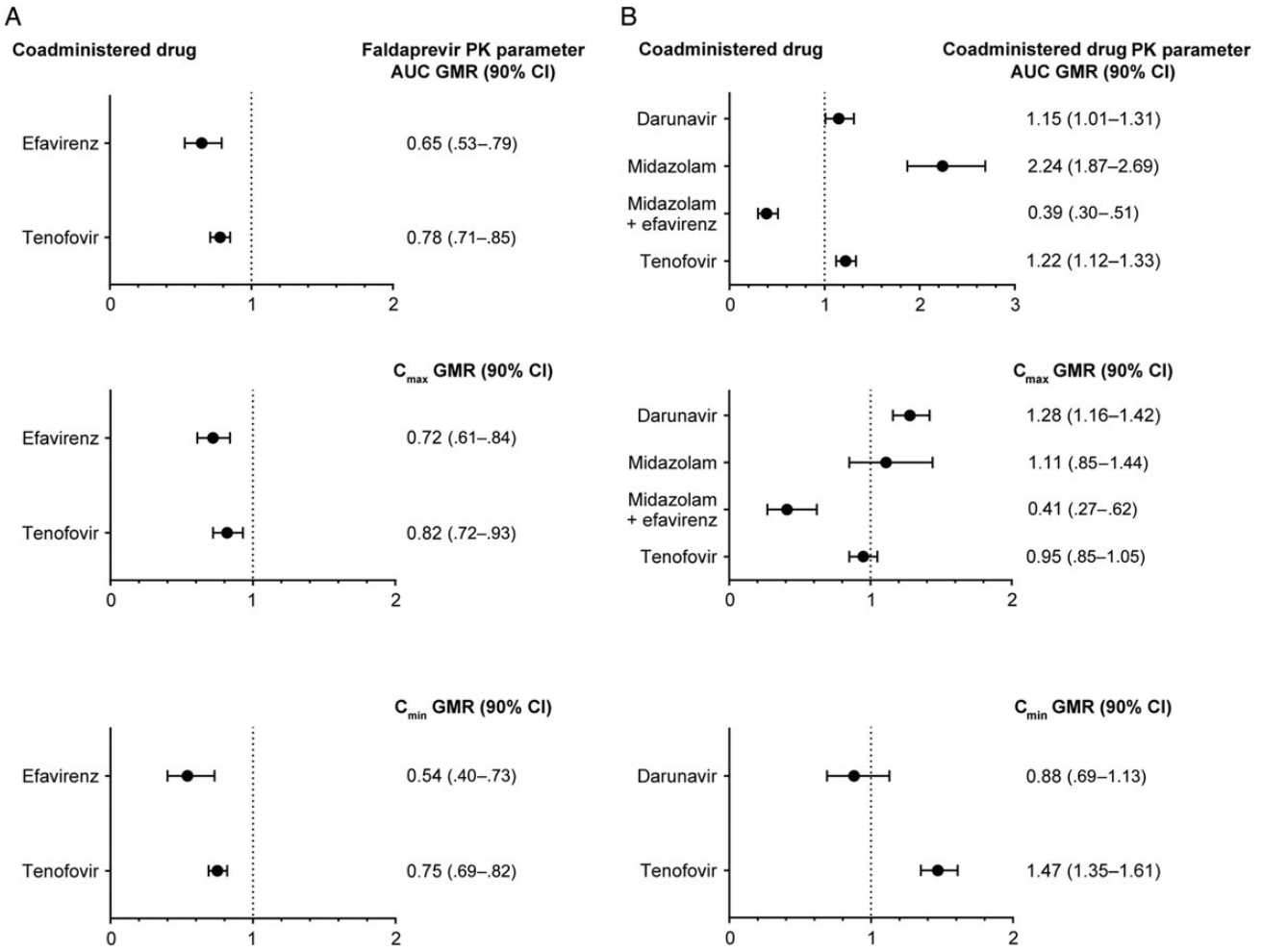

Figure 2. Pharmacokinetic effects of faldaprevir coadministered with darunavir/ritonavir, efavirenz, tenofovir, and midazolam. *A*, Adjusted GMR (90% CI) of faldaprevir AUC, C_{max}, and C_{min} (see Abbreviations for definitions) with/without coadministered drug (adjusted for effects in analysis of variance model). *B*, Adjusted GMR (90% CI) of coadministered drug AUC, C_{max}, and C_{min} with/without administration of faldaprevir. Abbreviations: AUC, area under the concentration–time curve; CI, confidence interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic.

Four subjects discontinued study treatment because of an AE, including 2 subjects (a male and a female) receiving faldaprevir alone in the tenofovir study (1 due to mild rash and the other due to moderate myalgia) and 2 subjects (a male and a female) receiving efavirenz, faldaprevir, and midazolam (1 due to moderate rash, and 1 due to moderate rash with mild transient elevation in alanine aminotransferase and aspartate aminotransferase). Consistent with the known inhibition by faldaprevir of uridine diphospho-glucuronosyltransferase 1A1 activity and unconjugated bilirubin uptake in the liver [18], total bilirubin concentrations in plasma increased during faldaprevir treatment. Mean total bilirubin concentrations increased between baseline and last treatment from 8.5 to 19.1 μmol/L in the darunavir/ritonavir study, from 9.7 to 32.9 μmol/L in the efavirenz study, and from 13.6 to 67.8 μmol/L in the tenofovir study. In all studies, bilirubin increased with increasing concentrations of faldaprevir; however, these elevations rapidly returned to normal after treatment was completed and were generally not associated with alanine aminotransferase, aspartate aminotransferase, or γ-glutamyl transferase elevations. The observations in bilirubin reported here are consistent with those seen in previous faldaprevir studies [2, 3]. As such, faldaprevir-associated increase in bilirubin is not considered clinically relevant. There were no clinically relevant changes in any other laboratory parameters or vital signs, and no abnormal ECG findings.

DISCUSSION

Treatment guidelines recommend starting HCV treatment in HIV/HCV-coinfected patients in whom HIV is stably

Table 4. Adverse Events, Irrespective of Causality, Occurring in >1 Patient

Adverse Event	Darunavir/ Ritonavir Study (n = 14)	Efavirenz Study (n = 15)	Tenofovir Study (n = 16)
Any adverse event	11 (78.6)	15 (100)	16 (100)
Any moderate adverse event	4 (28.6)	11 (73.3)	3 (18.8)
Any severe adverse event	0	0	0
Gastrointestinal disorders			
Diarrhea	6 (42.9)	4 (26.7)	8 (50.0)
Abdominal distension	4 (28.6)	0	0
Nausea	2 (14.3)	8 (53.3)	6 (37.5)
Flatulence	1 (7.1)	0	0
Vomiting	1 (7.1)	2 (13.3)	5 (31.5)
Abdominal pain	0	2 (13.3)	0
Upper abdominal pain	0	0	2 (12.5)
Dry mouth	0	2 (13.3)	0
Nervous system disorders			
Headache	4 (28.6)	5 (33.3)	10 (62.5)
Dizziness	1 (7.1)	12 (80.0)	1 (6.3)
Disturbance in attention	0	2 (13.3)	0
Psychiatric disorders			
Sleep disorder	1 (7.1)	3 (20.0)	0
Abnormal dreams	0	4 (26.7)	0
General disorders and administration site conditions			
Fatigue	3 (21.4)	5 (33.3)	0
Malaise	0	0	3 (18.8)
Feeling hot	0	3 (20.0)	0
Metabolism and nutrition disorders			
Decreased appetite	1 (7.1)	0	2 (12.5)
Eye disorders			
Ocular icterus	0	6 (40.0)	5 (31.3)
Hepatobiliary disorders			
Jaundice	0	6 (40.0)	5 (31.3)
Musculoskeletal and connective tissue disorders			
Myalgia	0	0	7 (43.8)
Arthralgia	0	0	2 (12.5)
Skin and subcutaneous tissue disorders			
Rash	0	7 (46.7)	1 (6.3)
Hyperhidrosis	0	2 (13.3)	0
Injury, poisoning, and procedural complications			
Sunburn/thermal burn	0	2 (13.1)	0

Data are presented as No. (%).

controlled with cART [11]. Therefore, effective HCV direct-acting antiviral agents that have a low potential for drug–drug interactions with ARVs could be highly beneficial for the treatment of HIV/HCV-coinfected individuals. In the 3 phase 1 studies in healthy volunteers described here, potential drug–drug interactions between faldaprevir and commonly used ARVs were examined in an effort to provide dosing recommendations for patients receiving faldaprevir in combination with peg-IFN and RBV plus darunavir/ritonavir, efavirenz, or tenofovir in the pivotal phase 3 trial in coinfected patients (STARTVerso4). In all studies, faldaprevir coadministered with ARVs was well tolerated and AEs were predominantly mild in intensity.

Coadministration of faldaprevir 240 mg twice daily with efavirenz in healthy volunteers resulted in an approximate 35% reduction in faldaprevir AUC and 46% reduction in faldaprevir C_{min} due to CYP3A induction by efavirenz. Despite induction of CYP3A by efavirenz, coadministration of efavirenz had no impact on the metabolite profile of faldaprevir in plasma (data not shown). The predominant metabolites of faldaprevir are M2a and M2b; their formation via CYP3A4/5 and clearance from the circulation have been described in a recent publication [19]. Both metabolites have a low permeability, and thus are not expected to diffuse readily into the blood or be absorbed effectively by the gastrointestinal tract. Rapid uptake into the liver by hepatic uptake transporters was also noted. In the presence of efavirenz, where faldaprevir clearance is increased, the low levels of metabolites permeating into the blood, combined with the efficient clearance into bile from the liver, is likely to be the reason that the levels of these metabolites in plasma remained unchanged. Clinical doses of faldaprevir that have been investigated in HCV genotype 1–infected patients are 120 and 240 mg once daily. In STARTVerso4, faldaprevir was utilized at the 240 mg once-daily dose when coadministered with efavirenz based on the decrease in faldaprevir exposure presented here. Preliminary data from STARTVerso4 suggest that this combination is effective and the safety profile is similar to that observed in HCV genotype 1–monoinfected patients [4]. Faldaprevir 240 mg once daily would therefore be the appropriate dose when coadministered with efavirenz in HIV/HCV-coinfected patients.

Faldaprevir 240 mg once daily had no clinically relevant effect on darunavir exposure when coadministered with darunavir/ritonavir (15% increase in darunavir AUC). Ritonavir is a moderate-to-strong in vivo inhibitor of CYP3A, depending on dose and regimen [16]. Darunavir is mainly metabolized by CYP3A and ritonavir is used to boost darunavir exposure by inhibition of CYP3A [20]. Faldaprevir is a substrate of CYP3A; thus, ritonavir is likely to also increase faldaprevir exposure. Preliminary data from STARTVerso4 suggest that faldaprevir 120 mg once daily coadministered with darunavir/ritonavir is effective and the safety profile is similar to that observed in HCV genotype 1–monoinfected patients [4]. Together, these results suggest that faldaprevir 120 mg once daily would be an appropriate dose to use in combination with darunavir/ritonavir.

The observed small, 2-sided interaction between faldaprevir and tenofovir was not considered to be clinically relevant (22% decrease in faldaprevir AUC; 22% increase in tenofovir

AUC), and the values are in line with the increases in PK parameters seen when tenofovir is coadministered with lopinavir and ritonavir (AUC, 32% increase; C_{max}, no change; C_{min}, 51% increase), and darunavir and ritonavir (AUC, 22% increase; C_{min}, increase 37%) where no dose adjustment is indicated [17]. Therefore, we do not consider faldaprevir dose adjustment to be necessary when coadministered with tenofovir. In STARTVerso4, tenofovir was used as part of the backbone therapy in patients treated with a lower dose of faldaprevir (120 mg once daily and 240 mg once daily) without any particular safety concerns and, therefore, either faldaprevir 120 or 240 mg once daily would be considered appropriate doses to use in combination with tenofovir [4]. In patients with renal impairment, close monitoring of kidney function and dose reduction of tenofovir is recommended [17], so the potential increase in tenofovir-related events with the increased exposure would be reduced when coadministered with faldaprevir.

The type and magnitude of drug–drug interaction varies depending on which HCV protease inhibitor is coadministered with ARVs. The NS3/4A HCV protease inhibitors boceprevir and telaprevir are strong CYP3A inhibitors and CYP3A substrates, and clinically relevant drug–drug interactions with ARVs and contraindications for coadministration with specific ARVs are well documented [21–23]. Coadministration of boceprevir and efavirenz is not recommended, whereas dose adjustments are required when efavirenz is coadministered with telaprevir [21–24]. Neither boceprevir nor telaprevir is recommended to be administered in combination with darunavir/ritonavir because of decreases in exposure of boceprevir (32%) and telaprevir (35%), and concomitant decreases in darunavir exposure (44% and 40%, respectively) [22–25]. The mechanisms for such unusual drug–drug interactions have not been clearly determined, but these effects cannot be explained by predictable mechanisms of CYP3A inhibition [26]. The HCV NS3/4A protease inhibitor simeprevir is a sensitive substrate of CYP3A and a mild inhibitor of intestinal CYP3A. Coadministration of simeprevir with efavirenz or ritonavir-boosted protease inhibitors such as darunavir/ritonavir is not recommended due to a significant decrease in simeprevir exposure with efavirenz and a significant increase in exposure with ritonavir [27, 28].

In summary, results of these phase 1 studies demonstrate that faldaprevir drug interactions with ARVs appear to be predictable based on the metabolism of faldaprevir by CYP3A and inhibition of CYP3A by faldaprevir and that any changes in faldaprevir exposure could be managed using either 120 mg once daily or 240 mg once daily.

Notes

Acknowledgments. The authors thank the research subjects; research staff of the Phase 1 Research Unit; University Hospital Basel, Switzerland; the Parexel Unit Berlin, Germany; and the Buffalo Clinical Research Center, Buffalo, New York.

Financial support. The authors received editorial support in the form of medical writing services from Simone Blagg of MediTech Media and Katrin Gudmundsdottir of Choice Healthcare Solutions, funded by Boehringer Ingelheim. This work was supported by Boehringer Ingelheim Pharma GmbH & Co KG.

Potential conflicts of interest. C. B., M. H., and R. F. received funding from Boehringer Ingelheim for conducting the studies. B. G., B. L., J. P. S., M. E., M. S., U. F., and Y. L. are employees of Boehringer Ingelheim. J. K. is a former employee of Boehringer Ingelheim and a current employee of AbbVie Inc. M. B. has participated in advisory boards for Bristol-Myers Squibb, Gilead, Janssen, and MSD and has received research grants from Bristol-Myers Squibb, Janssen, and MSD.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. White PW, Llinas-Brunet M, Amad M, et al. Preclinical characterization of BI 201335, a C-terminal carboxylic acid inhibitor of the hepatitis C virus NS3-NS4A protease. Antimicrob Agents Chemother **2010**; 54:4611–8.
2. Manns MP, Bourliere M, Benhamou Y, et al. Potency, safety, and pharmacokinetics of the NS3/4A protease inhibitor BI201335 in patients with chronic HCV genotype-1 infection. J Hepatol **2011**; 54:1114–22.
3. Ferenci P, Asselah T, Foster GR, et al. Faldaprevir plus pegylated interferon alfa-2a and ribavirin in chronic HCV genotype-1 treatment-naïve patients: final results from STARTVerso1, a randomised, double-blind, placebo-controlled phase III trial. In: 48th Annual Meeting of the European Association for the Study of the Liver, **2013**. Abstract 1416.
4. Rockstroh JK, Nelson M, Soriano V, et al. STARTVerso4 phase III trial of faldaprevir once-daily plus peg interferon α-2a and ribavirin (PR) in patients with HIV and HCV genotype-1 co-infection. In: 14th European AIDS Conference, **2013**. Abstract PS9/7.
5. de Lédinghen V, Barreiro P, Foucher J, et al. Liver fibrosis on account of chronic hepatitis C is more severe in HIV-positive than HIV-negative patients despite antiretroviral therapy. J Viral Hepat **2008**; 15: 427–33.
6. Reiberger T, Ferlitsch A, Sieghart W, et al. HIV-HCV coinfected patients with low CD4+ cell nadirs are at risk for faster fibrosis progression and portal hypertension. J Viral Hepat **2010**; 17:400–9.
7. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis **2001**; 33:562–9.
8. Sulkowski MS. HCV therapy in HIV-infected patients. Liver Int **2013**; 33(suppl 1):63–7.
9. European AIDS Clinical Society. Guidelines version 7.0, **2013**. Available at: http://eacsociety.org/Portals/0/Guidelines_Online_131014.pdf. Accessed 6 May 2014.
10. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, **2014**. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed 6 May 2014.
11. Thomas DL, Bartlett JG, Peters MG, Sherman KE, Sulkowski MS, Pham PA. Provisional guidance on the use of hepatitis C virus protease inhibitors for treatment of hepatitis C in HIV-infected persons. Clin Infect Dis **2012**; 54:979–83.
12. Sabo J, Kashuba ADM, Ballow CH, et al. Cytochrome P450 interactions with the HCV protease inhibitor faldaprevir (BI 201335) in healthy volunteers. In: The 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy, **2012**. Abstract A-1248.
13. Li Y, Ramsden D, Zhou J, Mao Y, Chen L, Tweedie D. Abundant metabolites found in excreta but not circulating in plasma—why and what

is the impact? In: 18th North American International Society for the Study of Xenobiotics meeting, **2012**. Poster 191.
14. Kort J. Clinical pharmacology update on the direct acting antivirals faldaprevir and BI 207127. In: Presentation at the 14th International Workshop on Clinical Pharmacology of HIV Therapy, Amsterdam, the Netherlands, 22–24 March, 2013.
15. Hsu A, Granneman GR, Bertz RJ. Ritonavir. Clinical pharmacokinetics and interactions with other anti-HIV agents. Clin Pharmacokinet **1998**; 35:275–91.
16. US Food and Drug Administration. Drug interaction studies—study design, data analysis, implications for dosing, and labeling recommendations, **2012**. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf. Accessed 6 May 2014.
17. Gilead Sciences International Ltd. Viread 245 mg film-coated tablets. Summary of product characteristics, **2014**. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000419/WC500051737.pdf. Accessed 6 May 2014.
18. Sane R, Podila L, Mathur A, et al. Mechanisms of isolated unconjugated hyperbilirubinaemia induced by the HCV NS3/4A protease inhibitor BI 201335. J Hepatol **2011**; 54:S488. Abstract 1236.
19. Li Y, Zhou J, Ramsden D, et al. Enzyme-transporter interplay: Effect transporter interplay: effect on the formation and clearance of abundant metabolites of faldaprevir found in excreta but not in circulation. Drug Metab Dispos **2014**; 42:384–93.
20. Hull MW, Montaner JS. Ritonavir-boosted protease inhibitors in HIV therapy. Ann Med **2011**; 43:375–88.
21. Wilby KJ, Greanya ED, Ford JA, Yoshida EM, Partovi N. A review of drug interactions with boceprevir and telaprevir: implications for HIV and transplant patients. Ann Hepatol **2012**; 11:179–85.
22. Merck Sharp & Dohme Corp. Victrelis prescribing information. **2011**, Available at: http://www.merck.com/product/usa/pi_circulars/v/victrelis/victrelis_pi.pdf. Accessed 6 May 2014.
23. Vertex Pharmaceuticals Inc. Incivek prescribing information, **2011**. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf. Accessed 6 May 2014.
24. van Heeswijk RP, Vandervoorde A, Boogaerts G, et al. Pharmacokinetic interactions between ARV agents and the investigational HCV protease inhibitor TVR in healthy volunteers. In: 18th Conference on Retroviruses and Opportunistic Infections, **2012**. Abstract 119.
25. Hulskotte EG, Feng HP, Xuan F, et al. Pharmacokinetic interactions between the hepatitis C virus protease inhibitor boceprevir and ritonavir-boosted HIV-1 protease inhibitors atazanavir, darunavir, and lopinavir. Clin Infect Dis **2012**; 56:718–26.
26. Kiser JJ, Burton JR, Anderson PL, Everson GT. Review and management of drug interactions with boceprevir and telaprevir. Hepatology **2012**; 55:1620–8.
27. Ouwerkerk-Mahadevan S, Sekar V, Simion A, Peeters M, Beumont-Mauviel M. The pharmacokinetic interactions of the HCV protease inhibitor simeprevir (TMC435) with HIV antiretroviral agents in healthy volunteers. In: Infectious Disease Society of America, San Diego, **2012**. Abstract 36620.
28. Karageorgopoulous DE, El-Sherif O, Bhagani S, Khoo SH. Drug interactions between antiretrovirals and new or emerging direct-acting antivirals in HIV/hepatitis C virus coinfection. Curr Opin Infect Dis **2014**; 27:36–45.