OPEN

The Effects of Boceprevir and Telaprevir on the Pharmacokinetics of Maraviroc: An Open-Label, Fixed-Sequence Study in Healthy Volunteers

Manoli Vourvahis, PharmD, Anna Plotka, MSc,† Constantino Kantaridis, MD,‡ Annie Fang, MD, PhD,§ and Jayvant Heera, MD‖*

Objective: To evaluate the effects of boceprevir (BOC) and telaprevir (TVR) on the pharmacokinetics (PK) of maraviroc (MVC) in healthy volunteers.

Methods: In this open-label, fixed-sequence study, 14 volunteers received MVC 150 mg twice daily alone for 5 days (period 1), followed by MVC + BOC 800 mg 3 times daily and MVC + TVR 750 mg 3 times daily, each for 10 days in periods 2 and 3, respectively, with a ≥10-day wash-out. PK was analyzed on day 5 of period 1 and day 10 of periods 2 and 3. Safety was also assessed.

Results: Ratios of the adjusted geometric means (90% confidence intervals) for MVC area under the curve from predose to 12 hours, maximum plasma concentration, and plasma concentration at 12 hours were 3.02 (2.53 to 3.59), 3.33 (2.54 to 4.36), and 2.78 (2.40 to 3.23), respectively, for MVC + BOC versus MVC alone, and 9.49 (7.94 to 11.34), 7.81 (5.92 to 10.32), and 10.17 (8.73 to 11.85), respectively, for MVC + TVR versus MVC alone. PK profiles for MVC + BOC or TVR were consistent with historic values for BOC and TVR monotherapy. Adverse event incidence was higher with MVC + BOC and MVC + TVR versus MVC alone. Dysgeusia (50%) and pruritus (29%) occurred most commonly with MVC + BOC, and fatigue (46%) and headache (31%) with MVC + TVR. There were no serious adverse events.

Conclusions: MVC exposures were significantly increased with BOC or TVR, therefore MVC should be dosed at 150 mg twice daily when coadministered with these newly approved hepatitis C protease inhibitors. No dose adjustment for BOC or TVR is warranted with MVC. MVC + BOC or TVR was generally well tolerated with no unexpected safety findings.

Key Words: maraviroc, boceprevir, telaprevir, pharmacokinetics, drug interaction

(*J Acquir Immune Defic Syndr* 2014;65:564–570)

INTRODUCTION

Maraviroc (MVC) is a first-in-class selective chemokine coreceptor type-5 (CCR5) antagonist indicated for the treatment of CCR5-tropic (R5) HIV-1 infection in both treatment-naive and treatment-experienced patients in the United States,[1] and in treatment-experienced patients in the European Union.[2] MVC is primarily metabolized by hepatic cytochrome P450 (CYP) 3A enzymes, with negligible metabolic activity for other CYP enzymes and is also a substrate for the efflux transport P-glycoprotein (P-gp).[3] MVC exposures have been shown to increase significantly when coadministered with potent CYP3A/P-gp inhibitors.[3] As such, the recommended MVC dose in the presence of potent CYP3A/P-gp inhibitors is 150 mg twice daily (BID).[1,2]

Patients with HIV-1 infection are disproportionately affected by viral hepatitis, specifically hepatitis C virus (HCV), which can lead to life-threatening complications.[4] Approximately 25% of HIV-infected patients in the United States and Europe are coinfected with HCV, accounting for >75% of liver-related deaths in HIV-infected patients.[5] Boceprevir (BOC) and telaprevir (TVR) are newly approved HCV protease inhibitors indicated (in combination with pegylated interferon alpha and ribavirin) for the treatment of genotype 1 chronic HCV in adult patients with compensated liver disease.[6–9] BOC is a potent inhibitor of CYP3A, and TVR is also a potent inhibitor of CYP3A and an inhibitor of P-gp[6–9]; however, some unexpected drug interactions with HIV protease inhibitors have led to recommendations against the coadministration of BOC with darunavir/ritonavir, atazanavir/ritonavir, lopinavir/ritonavir, and fosamprenavir/ritonavir, and against the coadministration of TVR with darunavir/ritonavir, lopinavir/ritonavir, and fosamprenavir/ritonavir.[6–9]

Given the limited treatment options for HIV-1 and HCV coinfected patients, it is therefore important to investigate potential drug interactions of BOC and TVR with MVC. This study was conducted to estimate the effect of BOC 800 mg 3 times daily (TID) and TVR 750 mg TID on the

Received for publication August 8, 2013; accepted December 3, 2013.

From the *Clinical Pharmacology, Pfizer Inc, New York, NY; †Statistics, Pfizer Inc, Collegeville, PA; ‡Pfizer Clinical Research Unit, Brussels, Belgium; §Clinical Development, Pfizer Inc, New York, NY; and ‖Clinical Development, Pfizer Inc, Groton, CT.

Supported by ViiV Healthcare and managed by Pfizer Inc.

Presented at the 14th International Workshop on Clinical Pharmacology of HIV, April 23, 2013, Amsterdam, the Netherlands.

M.V., A.P., C.K., A.F., and J.H. are employees of Pfizer, Inc and hold stock/stock options in Pfizer, Inc.

Correspondence to: Manoli Vourvahis, PharmD, Pfizer Global Research and Development, 219 East 42nd Street, New York, NY 10017 (e-mail: manoli.vourvahis@pfizer.com).

pharmacokinetics (PK) of MVC, and to describe the PK of BOC and TVR when dosed in combination with MVC 150 mg BID. The safety and tolerability of MVC in combination with BOC and TVR was also assessed.

METHODS

Study Population

Eligible volunteers were healthy adults (aged 18–55 years) who had a body mass index of 17.5–30.5 kg/m^2, and a body weight of more than 50 kg. Volunteers who had used prescription or nonprescription drugs or dietary supplements within 7 days or 5 half-lives (whichever was longer) before the start of study treatment were not permitted to take part in the study. Volunteers who had used herbal supplements or hormonal methods of contraception within 28 days (6 months for Depo-Provera) were also not permitted to take part in the study. Volunteers with positive results for HIV-1, HIV-2, hepatitis B serology (hepatitis B surface antigen, hepatitis B core antibody), or anti-HCV serology (as determined by multi-antigen enzyme immunoassay), or who had a history of hypersensitivity to the study drugs, were excluded.

Study Design and Treatment

This was an open-label, fixed-sequence, phase I study (NCT01597895) conducted at a single site (Pfizer Clinical Research Unit, Brussels, Belgium). After a screening visit within 28 days before the start of treatment, volunteers received MVC 150 mg BID (every 12 hours) for 5 days (treatment period 1), followed by MVC 150 mg BID plus BOC 800 mg TID (every 8 hours) for 10 days (treatment period 2), then MVC 150 mg BID plus TVR 750 mg TID (every 8 hours) for 10 days (treatment period 3), with a ≥10-day wash-out between periods 2 and 3 (Fig. 1).

Study treatment was administered with 240 mL water at ambient temperature 30 minutes after a standard fat meal/snack (approximately 20 g fat and ≥500 calories). On PK assessment days (day 5 of treatment period 1 and day 10 of treatment periods 2 and 3), volunteers ate a standardized breakfast containing approximately 20 g fat and 800–1000 calories and received only a single (morning) dose of MVC, as well as only the morning and afternoon doses of BOC and TVR. Study personnel conducted mouth checks to ensure treatment compliance. To standardize conditions on PK sampling days, all volunteers were required to refrain from lying down [except when required for vital signs and electrocardiogram (ECG) assessments] and eating and drinking beverages other than water during the first 4 hours after dosing.

Volunteers could be discontinued from the study at any time at their own request, or on the grounds of safety concerns, behavioral reasons, or inability to comply with the study activity or procedures, at the investigators' discretion.

This study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines established by the International Conference on Harmonization. The final protocol, amendments, and informed consent documentation were reviewed and approved by the study center institutional review board. All volunteers provided written, informed consent before participating in any study procedures.

Pharmacokinetic Assessment

Blood samples for MVC PK analysis were collected predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours postdose on day 5 of treatment period 1 (MVC) and on day 10 of treatment periods 2 (MVC and BOC) and 3 (MVC and TVR). Blood samples for BOC and TVR PK analysis were collected predose and at 0.5, 1, 2, 3, 4, 6, and 8 hours postdose on day 10 of treatment periods 2 and 3, respectively. Samples of 4 mL were taken to provide a minimum volume of 1.5 mL plasma for PK analysis and were transferred into appropriately labeled tubes containing sodium heparin (MVC), dipotassium ethylenediaminetetra-acetic acid (K_2EDTA) (BOC), or tripotassium ethylenediaminetetra-acetic acid (K_3EDTA) (TVR). All samples were centrifuged at approximately 1700 g for approximately 10 minutes at 4°C. For MVC and BOC, plasma was extracted and stored in appropriately labeled screw-capped polypropylene tubes at approximately −20°C (MVC) or −70°C (BOC) within 1 hour of collection. Plasma extraction for TVR followed the same process, although after centrifugation approximately 1 mL plasma was transferred to an appropriately labeled screw-capped polypropylene tube containing 0.05 mL of 10% formic acid, before mixing thoroughly and being stored at approximately −70°C. Formic acid solution was added to plasma to allow for accurate quantification of TVR by preventing TVR epimerization.

Plasma samples were analyzed for MVC (Tandem Labs, West Trenton, NJ),[10] and for BOC and TVR (Covance Bioanalytical Services, Shanghai, China), using a solid-phase extraction and a validated high-performance liquid chromatography/dual mass spectrometry assay.

Noncompartmental analyses were performed using standard methods with eNCA version 2.2 (Pfizer, Inc, New York, NY). Area under the plasma concentration–time curve (AUC) from predose (0 hours) to 12 hours (AUC_{12}; MVC) or 8 hours postdose (AUC_8; BOC and TVR) was determined by the linear/log trapezoidal method, whereas plasma

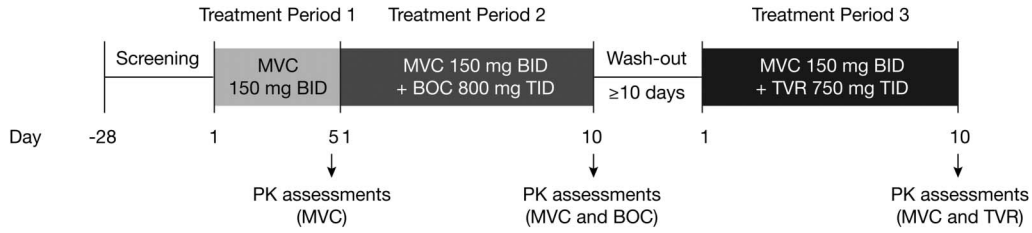

FIGURE 1. Study design.

concentration at 12 hours (C_{12}; MVC) or 8 hours postdose (C_8; BOC and TVR), maximum plasma concentration (C_{max}), and time to C_{max} (T_{max}) were determined by direct observation.

Safety and Tolerability

All observed and volunteered adverse events (AEs) were recorded and assessed by the investigator for severity and relationship to study treatment. Additional safety assessments included standard hematology, urinalysis, and chemistry laboratory assessments, physical examinations, vital signs (blood pressure and pulse) measurements, and ECGs. Orthostatic hypotension, a concentration-dependent AE observed with MVC,[11] was defined as a decrease of ≥20 mm Hg for systolic blood pressure or ≥10 mm Hg for diastolic blood pressure 2 minutes after standing from a supine position, and may have been symptomatic or asymptomatic.

Sample Size

A minimum sample size of 12 volunteers was required to provide 90% confidence intervals (CIs) for the difference between treatments on the natural logarithmic scale of ±0.1536 for MVC AUC_{12}, ±0.2745 for MVC C_{max}, and ±0.1493 for MVC C_{12}, with 80% coverage probability. To allow for any volunteers who might not complete the study, 14 volunteers were enrolled.

Construction of 90% CIs was chosen based on FDA Guidance "Statistical Approaches to Establishing Bioequivalence."[12] Because of the nature of normal-theory construction of 90% CIs, this corresponds to performing 2 one-sided tests hypothesis at the 5% level of significance.

Statistical Analysis

Natural log-transformed AUC_{12}, C_{max}, and C_{12} for MVC were analyzed using a mixed effect model with treatment as fixed effect and subject as a random effect. MVC alone was the reference treatment, and MVC plus BOC and MVC plus TVR were the test treatments. Estimates of the adjusted mean differences (Test–Reference) and corresponding 90% CIs were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

BOC and TVR PK data were summarized descriptively and compared with mean historical minimum plasma concentrations (C_{min}) data (102 ng/mL and 1802 ng/mL, respectively).[1,13–16] BOC and TVR data were determined to be comparable with the historical data if the mean C_8 for both agents fell within the 50% range of their historical C_{min} values: 51–204 ng/mL for BOC and 901–3604 ng/mL for TVR, based on simulations. Safety data were summarized descriptively.

RESULTS

Study Population

A total of 14 volunteers were enrolled and treated. All 14 completed treatment periods 1 and 2, but 1 volunteer withdrew during the wash-out period (between periods 2 and 3) because of an AE (severe asthmatic crisis) that was not considered to be related to treatment, and thus did not participate in treatment period 3.

All volunteers were men with a mean age (SD) of 33.3 years. The majority (n = 12/14, 85.7%) were white with the remaining 2 volunteers (14.3%) being of other races (one of Hispanic ethnicity and one of Asian ancestry). Volunteers had a mean (SD) weight of 79.3 (11.4) kg and body mass index of 24.4 (2.8) kg/m^2.

Bioanalytical Summary

Calibration standard responses were linear over the range of 0.5–500 ng/mL for MVC, 25–2500 ng/mL for BOC, and 50–5000 ng/mL for TVR. The between-day assay accuracy, expressed as percent relative error for quality-control concentrations in the low, medium, and high-diluted quality control samples ranged from 4.6%–7.3% for MVC, −5.2%–3.7% for BOC, and −0.6%–0.8% for TVR. Assay precision, expressed as the between-day percent coefficient of variation (%CV) of the mean estimated concentrations of quality-control samples, was ≤7.4% for the low (1.5 ng/mL), medium (50 and 150 ng/mL), high (375 ng/mL), and diluted (375 ng/mL) concentrations of MVC. Assay precision (%CV) for BOC was ≤5.6% for the low (75 ng/mL), medium (250 ng/mL), high (1800 ng/mL), and diluted (12,500 ng/mL) concentrations, and for TVR was ≤3.8% for the low (150 ng/mL), medium (500 ng/mL), high (3600 ng/mL), and diluted (25,000 ng/mL) concentrations.

Plasma MVC PK

MVC plasma exposure (based on AUC_{12} and C_{max}) was increased by approximately 3-fold in the presence of BOC, and by approximately 8- to 9-fold in the presence of TVR (Table 1; Fig. 2). MVC C_{12} values were approximately 3-fold higher for MVC plus BOC (66.1 ng/mL), and approximately 10-fold higher for MVC plus TVR (235.5 ng/mL), when compared with MVC alone (23.8 ng/mL).

Intersubject variability for MVC, as measured by the geometric %CV for AUC_{12}, C_{max}, and C_{12} was 24%–36% when MVC was coadministered with either BOC or TVR (Table 1).

C_{max} was achieved within a median T_{max} of 2.0 (range, 1.0–6.0) hours when MVC was administered alone, 2.0 (range, 0.5–3.0) hours when MVC was administered with BOC, and 3.0 (range, 2.0–4.0) hours when MVC was given with TVR.

Plasma BOC and TVR PK

When coadministered with MVC, BOC and TVR exposures were consistent with historical data (Table 2), indicating that MVC had no notable impact on the PK profile of BOC and TVR.

Safety and Tolerability

AE incidence was higher during treatment with MVC plus BOC (100%) and MVC plus TVR (92%) compared with

TABLE 1. Geometric Means and Adjusted Geometric Mean Ratios for MVC PK Parameters Alone and in the Presence of BOC and TVR

	Geometric Mean (%CV)		Ratio of Adjusted Geometric Mean (90% CI)
	MVC + BOC (N = 14)	MVC Alone (N = 14)	MVC + BOC Versus MVC Alone
MVC 150 mg BID + BOC 800 mg TID versus MVC 150 mg BID			
AUC_{12} (ng·h/mL)	1807 (30)	598.8 (55)	3.02 (2.53 to 3.59)
C_{12} (ng/mL)	66.1 (32)	23.8 (41)	2.78 (2.40 to 3.23)
C_{max} (ng/mL)	369.8 (36)	111.2 (111)	3.33 (2.54 to 4.36)
	TVR + MVC (N = 13)	**MVC Alone (N = 14)**	**MVC + TVR Versus MVC Alone**
MVC 150 mg BID + TVR 750 mg TID versus MVC 150 mg BID			
AUC_{12} (ng·h/mL)	5580 (24)	598.8 (55)	9.49 (7.94 to 11.34)
C_{12} (ng/mL)	235.5 (25)	23.8 (41)	10.17 (8.73 to 11.85)
C_{max} (ng/mL)	858.1 (28)	111.2 (111)	7.81 (5.92 to 10.32)

AUC_{12}, area under the plasma concentration–time curve from predose to 12 hours postdose; C_{12}, plasma concentration at 12 hours postdose; C_{max}, maximum plasma concentration.

MVC alone (43%), and the majority of AEs were considered to be treatment-related (Table 3). The most common treatment-related AEs occurring during treatment with MVC alone, MVC plus BOC, and MVC plus TVR, respectively, were headache, dysgeusia, and fatigue, as summarized in Table 3. No events of postural hypotension or dizziness were reported in this study.

All AEs were mild to moderate in severity, with the exception of a severe event of asthmatic crisis following the completion of treatment period 2 (MVC plus BOC), which led to the discontinuation of 1 volunteer. This AE was not considered to be related to treatment but related to a pre-existing and undisclosed history of asthma. The event lasted 8 hours and resolved with treatment given.

There were no deaths, serious AEs, temporary discontinuations, or dose reductions because of AEs in this study. No clinically significant changes in laboratory parameters, vital signs, or ECGs were reported.

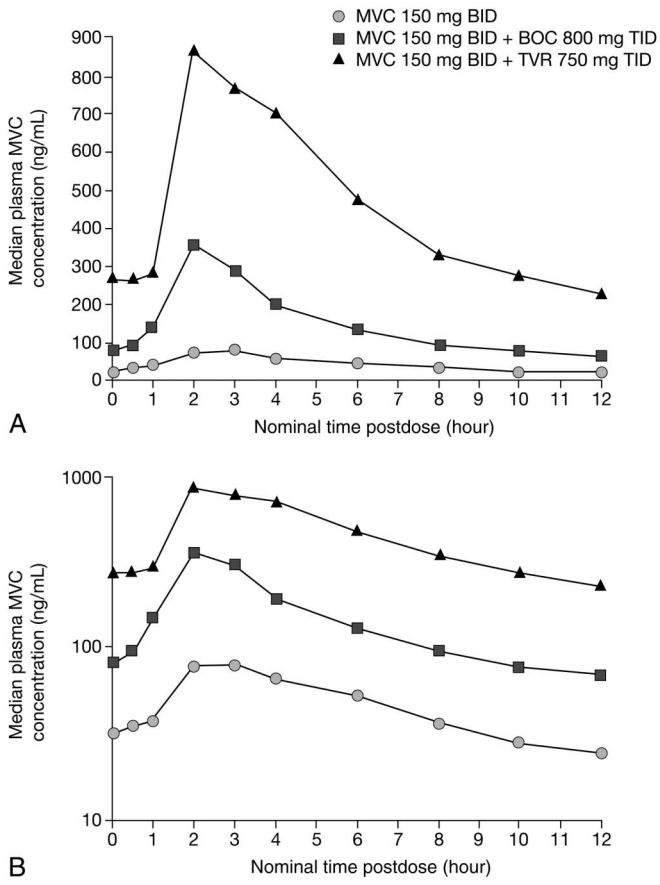

FIGURE 2. Median plasma-time MVC concentrations by treatment shown by (A) linear scale, and (B) semi-logarithmic scale.

DISCUSSION

A significant proportion of HIV-infected individuals are coinfected with HCV and consequently are at increased risk for severe liver disease.[5] As liver fibrogenesis may be caused by stimulation of CCR5 receptors, MVC, a CCR5 antagonist, may have a beneficial effect on liver fibrosis. There is, therefore, increasing interest in using MVC as part of treatment regimens for HIV/HCV coinfected patients. Preliminary data from investigators from the University of Brescia (Italy) demonstrated a significant improvement in liver stiffness in 54 patients over 24 weeks when MVC 150 mg BID was added to antiretroviral regimens compared with existing regimens alone ($P = 0.03$).[17] Furthermore, an ongoing study (NCT01327547) is primarily evaluating the safety of MVC in 120 HIV/HCV coinfected patients, as well as assessing the potential antifibrotic activity of MVC as a secondary objective.

BOC and TVR are newly approved HCV protease inhibitors that have been shown to cause significant drug interactions. As such, many HIV protease inhibitors are not recommended to be coadministered with either BOC or TVR, thus limiting treatment options in HIV/HCV coinfected patients.[6–9] The study reported in this article was designed to investigate the effect of coadministration of BOC 800 mg BID and TVR 750 mg TID on the PK of MVC 150 mg BID, and to describe the PK of BOC and TVR when dosed in combination with MVC. Our results confirm that, when

TABLE 2. Summary of Plasma BOC and TVR Pharmacokinetic Parameters in the Presence and Absence (Historical Studies) of MVC

	MVC + BOC (N = 14)*	BOC Alone[14,16] (N = 48)†	MVC + TVR (N = 13)*	TVR Alone[13,14] (N = 120)†
AUC_8 (ng·h/mL)	5404 (24)	5590 (4601–7070)	21,980 (24)	20,013 (18,157–22,300)
C_8 (ng/mL)	80.7 (34)	102 (88.5–111)	1943 (24)	1802 (1505–2030)
C_{max} (ng/mL)	1927 (32)	1701 (1423–2100)	3533 (23)	3250 (2969–3510)
T_{max} (h)	2.05 (1.00–4.00)	—	4.00 (1.00–4.02)	—

AUC_8, area under the plasma concentration–time curve from predose to 8 hours postdose; BOC, boceprevir 800 mg 3 times daily; C_8, plasma concentration at 8 hours postdose; C_{max}, maximum plasma concentration; CV, coefficient of variation; MVC, maraviroc 150 mg twice daily; T_{max}, time to C_{max}; TVR, telaprevir 750 mg 3 times daily.

*AUC_8, C_8, and C_{max} data reported as geometric mean (%CV); T_{max} data reported as median (range).

†AUC_8, C_8, and C_{max} data reported as arithmetic mean of the mean (range of mean) from historical studies.

coadministered with either BOC or TVR, overall MVC exposure is increased significantly.

TVR seemed to have a greater impact on MVC plasma exposure than BOC, as indicated by an 8- to 9-fold increase in both mean MVC AUC_{12} and C_{max} values after coadministration compared with a 3-fold increase with BOC. The greater increase in MVC exposures observed with TVR was expected, as TVR has been shown to increase the AUC of midazolam (a probe substrate for CYP3A) by 796% as compared with 430% with BOC after oral coadministration of midazolam and an increase in the AUC of digoxin (a probe for P-gp) by 85% as compared with 19% with BOC.[6,8] Furthermore, a potential mechanism for the magnitude of this interaction observed with TVR may be interplay between inhibition of CYP3A/P-gp and organic ion transporter 1B1 (OATP1B1) by TVR,[8] as MVC has been shown to be a substrate for OATP1B1.[18,19] In vitro data suggest that TVR is a more potent inhibitor of OATP1B1 with an IC_{50} of 2.2 μM compared with an IC_{50} of 18 μM for BOC.[20,21] Additionally, inhibition of OATP1B1 is more likely to occur in vivo with TVR given that the unbound C_{max}/OATP1B1 IC_{50} ratio for TVR is 0.95, whereas the ratio for BOC is only 0.04.[20,21] The combination of CYP3A/OATP1B1 inhibition by TVR was most likely also observed in a study where TVR was coadministered with atorvastatin, a substrate for both CYP3A and OATP1B1.[8,9] In this study, TVR increased the AUC of atorvastatin 7.88-fold whereas in a similar study, BOC only increased the exposure of atorvastatin 2.30-fold.[6–9]

The magnitude of the MVC interaction with TVR is also consistent with that observed in a previous drug interaction study where MVC was dosed in combination with saquinavir/ritonavir (SQV/r), where MVC exposures were increased 9.77-fold.[1,2] To date, TVR and SQV/r are the only 2 agents shown to increase the geometric mean MVC AUC greater than 5-fold. Similarly to TVR, SQV/r is a potent inhibitor of CYP3A (increases midazolam AUC 11.4-fold), an inhibitor of P-gp (increases digoxin AUC by 49%) and an inhibitor of OATP1B1 (IC_{50} = 2.1 μM).[22,23]

In the present study, MVC average concentrations (C_{avg}), when dosed at 150 mg BID in the presence of TVR and BOC, were 474 ng/mL and 151 ng/mL, respectively. The exposures seen in this study are within the exposure range observed in phase III clinical studies evaluating the efficacy and safety of MVC in patients with CCR5-topic HIV-1[24] and are at or above the C_{avg} exposure at which near maximal virologic efficacy is achieved with MVC (≥75–100 ng/mL).[25,26] These findings suggest that MVC should be dosed at 150 mg BID when coadministered with either BOC or TVR, consistent with current dose recommendations for MVC when dosed in combination with other potent CYP3A inhibitors.[1,2] However, as regulatory discussions are pending, we would suggest that prescribers should refer to your local prescribing

TABLE 3. Summary of Safety

	MVC Alone, N = 14	MVC + BOC, N = 14	MVC + TVR, N = 13
Volunteers with AEs, n (%)	6 (42.9)	14 (100.0)	12 (92.3)
Volunteers with treatment-related AEs, n (%)	6 (42.9)	14 (100.0)	12 (92.3)
Treatment-related AEs reported by ≥2 volunteers (any treatment)			
Abdominal pain	1 (7.1)	1 (7.1)	3 (23.1)
Anorectal discomfort	0 (0.0)	0 (0.0)	2 (15.4)
Change of bowel habit	2 (14.3)	3 (21.4)	2 (15.4)
Decreased appetite	0 (0.0)	0 (0.0)	3 (23.1)
Diarrhea	1 (7.1)	1 (7.1)	3 (23.1)
Dysgeusia	0 (0.0)	7 (50.0)	0 (0.0)
Fatigue	0 (0.0)	2 (14.3)	6 (46.2)
Headache	3 (21.4)	2 (14.3)	4 (30.8)
Paresthesia	0 (0.0)	2 (14.3)	1 (7.7)
Pruritus	0 (0.0)	4 (28.6)	1 (7.7)

information for MVC dosing recommendations with BOC and TVR in their region.

As with most drug–drug interaction studies, healthy volunteers, rather than patients, were enrolled in this study. MVC is primarily metabolized by the liver and therefore exposures have the potential to be higher in HIV/HCV coinfected patients with hepatic impairment, as hepatic damage and disease may affect CYP enzyme activity.[27–32] A study conducted in HIV-negative subjects with hepatic impairment demonstrated that MVC exposures in subjects with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment had a geometric mean 25% (mild) and 46% (moderate) greater AUC_{last} and a 11% (mild) and 32% (moderate) greater C_{max} relative to subjects with normal hepatic function[33] after a single dose of MVC 300 mg. As such, patients with moderate hepatic impairment receiving MVC with potent CYP3A inhibitors, such as BOC, should be monitored closely.[1,2] Currently, TVR is not recommended to be dosed in patients with moderate and severe hepatic impairment.[8,9] No exposure data are available for MVC in severe hepatic impairment, thus no recommendation in this population can be given at this time.

In this study, MVC did not seem to cause clinically significant changes in concentrations of either BOC or TVR as the mean PK exposures of BOC (AUC_8 5404 ng·h/mL; C_8 80.7 ng/mL) and TVR (AUC_8 21980 ng·h/mL; C_8 1943 ng/mL) after MVC coadministration were consistent with those previously reported when BOC (AUC_8 4601–7070 ng·h/mL; C_8 88.5–111 ng/mL) and TVR (AUC_8 18157–22300 ng·h/mL; C_8 1505–2030 ng/mL) were dosed alone.[1,13–16] These findings suggest that no dose adjustment for BOC or TVR is warranted when coadministered with MVC.

Finally, MVC coadministered with BOC or TVR was generally well tolerated among the small population of healthy volunteers in this study. Although AE incidence was higher during combination treatment, the majority of AEs were mild or moderate in severity, and there were no serious AEs, discontinuations because of treatment-related AEs, or deaths during the study. The most frequently experienced AEs were dysgeusia and pruritus for the MVC plus BOC combination, and headache and fatigue for the MVC plus TVR combination. Fatigue, dysgeusia, and pruritus seemed to be unique to the coadministration of MVC plus BOC or MVC plus TPV and were consistent with previous findings for BOC or TPV alone.[6–9] No postural hypotension or dizziness was reported in this study despite the significant increases in MVC exposures when coadministered with BOC or TVR.

CONCLUSIONS

In summary, MVC exposure was increased in the presence of BOC or TVR. These findings are consistent with evidence that both BOC and TVR are potent inhibitors of CYP3A, and support dosing of MVC at 150 mg BID when coadministered with either BOC or TVR. When coadministered with MVC, BOC and TVR exposures were consistent with historical BOC and TVR monotherapy data; therefore, no dose adjustment for BOC or TVR is warranted with MVC. MVC coadministered with BOC or TVR was generally well tolerated with no unexpected safety findings.

ACKNOWLEDGMENTS

Editorial support was provided by Lynsey Stevenson of Complete Medical Communications.

REFERENCES

1. ViiV Healthcare. Selzentry (maraviroc) prescribing information. Available at: http://www.viivhealthcare.com/~/media/Files/G/GlaxoSmithKline-Plc/pdfs/us_selzentry.pdf. Accessed April 3, 2013.
2. ViiV Healthcare. Celsentri (maraviroc) summary of product characteristics. Available at: http://www.viivhealthcare.com/products/selzentry-celsentri.aspx#. Accessed April 3, 2013.
3. Abel S, Back DJ, Vourvahis M. Maraviroc: pharmacokinetics and drug interactions. *Antivir Ther.* 2009;14:607–618.
4. Centers for Disease Control and Prevention. HIV and viral hepatitis. Available at: http://www.cdc.gov/hiv/resources/factsheets/hepatitis.htm. Accessed April 3, 2013.
5. Puoti M, Manno D, Nasta P, et al. The burden of HIV and hepatitis C virus coinfection. *Curr Opin HIV AIDS.* 2007;2:460–465.
6. Merck Sharp & Dohme Corp. Victrelis (boceprevir) prescribing information. Available at: http://www.merck.com/product/usa/pi_circulars/v/victrelis/victrelis_pi.pdf. Accessed April 3, 2013.
7. Merck Sharp & Dohme Ltd. Victrelis (boceprevir) summary of product characteristics. Available at: http://www.medicines.org.uk/emc/medicine/24768/SPC/. Accessed April 3, 2013.
8. Vertex Pharmaceuticals Inc. Incivek (telaprevir) prescribing information. Available at: http://pi.vrtx.com/files/uspi_telaprevir.pdf. Accessed April 3, 2013.
9. Janssen-Cilag Ltd. Incivo (telaprevir) summary of product characteristics. Available at: http://www.medicines.org.uk/emc/medicine/25038/SPC/. Accessed April 3, 2013.
10. Brewer E, Felix T, Clarke P, et al. An LC-MS-MS method for quantitative determination of maraviroc (UK-427,857) in human plasma, urine and cerebrospinal fluid. *Biomed Chromatogr.* 2010;24:1316–1323.
11. Weatherley B, Vourvahis M, McFadyen L. Modeling of maraviroc pharmacokinetics in the presence of atazanavir/ritonavir in healthy volunteers and HIV-1-infected patients. Abstract presented at: 12th International Workshop on Clinical Pharmacology of HIV Therapy; April 13–15, 2011; Miami, FL.
12. U.S. Department of Health and Human Services FaDACfDEaRC. Guidance for Industry: Statistical Approaches to establishing Bioequivalence. Available at: http://www.fda.gov/downloads/Drugs/Guidances/ucm070244.pdf. Accessed January 2, 2014.
13. Garg V, van Heeswijk R, Yang Y, et al. The pharmacokinetic interaction between an oral contraceptive containing ethinyl estradiol and norethindrone and the HCV protease inhibitor telaprevir. *J Clin Pharmacol.* 2012;52:1574–1583.
14. Center for Drug Evaluation and Research. Boceprevir: Application number 202258Orig1s000. Other reviews. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202258Orig1s000OtherR.pdf. Accessed April 4, 2013.
15. Center for Drug Evaluation and Research. Telaprevir: Application number 201917Orig1s000. Clinical pharmacology and biopharmaceutics review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201917Orig1s000ClinPharmR.pdf. Accessed April 4, 2013.
16. Hammond KP, Wolfe P, Burton JR Jr, et al. Pharmacokinetic interaction between boceprevir and etravirine in HIV/HCV seronegative volunteers. *J Acquir Immune Defic Syndr.* 2013;62:67–73.
17. Nasta P, Gatti F, Borghi F, et al. Maraviroc (MVC) reduces liver stiffness (LS) in HIV-hepatitis C (HCV) co-infected patients. Abstract presented at: 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 17–20, 2013; Rome, Italy.
18. Siccardi M, D'Avolio A, Nozza S, et al. Maraviroc is a substrate for OATP1B1 in vitro and maraviroc plasma concentrations are influenced by SLCO1B1 521 T>C polymorphism. *Pharmacogenet Genomics.* 2010;20:759–765.

19. Vourvahis M, Sanders F, Malarstig A, et al. Impact of genetic variants of OATP1B1 (SLCO1B1) on maraviroc pharmacokinetics. Poster PE6.4 presented at: European AIDS Conference; October 12–15, 2011; Belgrade, Serbia.
20. Kunze A, Huwyler J, Camenisch G, et al. Interaction of the antiviral drug telaprevir with renal and hepatic drug transporters. Available at: Biochem.Pharmacol.
21. Center for Drug Evaluation and Research. Boceprevir: Application number 202258Orig1s000. Other reviews. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202258orig1s000clinpharmr.pdf. Accessed November 19, 2013.
22. Roche Farma SALS. Invirase (saquinavir mesylate) summary of product characteristics. Available at: http://www.gene.com/download/pdf/Invirase%20PI%20November%202012%20%281%29.pdf. Accessed November 19, 2013.
23. Annaert P, Ye ZW, Stieger B, et al. Interaction of HIV protease inhibitors with OATP1B1, 1B3, and 2B1. *Xenobiotica*. 2010;40:163–176.
24. Weatherley B, McFadyen L, Chan PLS, et al. Population pharmacokinetic covariate analysis of maraviroc in Phase 2b/3 studies in treatment experienced (TE) HIV-1 infected subjects on optimized background therapy (OBT). Poster 17a presented at: 9th International Workshop on Clinical Pharmacology of HIV Therapy; April 7–9, 2008; New Orleans, LA.
25. McFadyen L, Jacqmin P, Wade JR, et al. Maraviroc (MVC) exposure–efficacy relationship in treatment-experienced HIV-1-infected patients. Poster P4.1/06 presented at: 11th European AIDS Conference; October 24–27, 2007; Madrid, Spain.
26. McFadyen L, Jacqmin P, Weatherley B, et al. Lack of adherence to treatment drives maraviroc exposure response in the MERIT study in treatment naive subjects. Poster presented at: 11th International Workshop on Clinical Pharmacology of HIV Therapy; April 7–9, 2010; Sorrento, Italy.
27. Kolwankar D, Vuppalanchi R, Ethell B, et al. Association between nonalcoholic hepatic steatosis and hepatic cytochrome P-450 3A activity. *Clin Gastroenterol Hepatol.* 2007;5:388–393.
28. Donato MT, Lahoz A, Jimenez N, et al. Potential impact of steatosis on cytochrome P450 enzymes of human hepatocytes isolated from fatty liver grafts. *Drug Metab Dispos.* 2006;34:1556–1562.
29. Ohnishi A, Murakami S, Akizuki S, et al. In vivo metabolic activity of CYP2C19 and CYP3A in relation to CYP2C19 genetic polymorphism in chronic liver disease. *J Clin Pharmacol.* 2005;45:1221–1229.
30. Villeneuve JP, Pichette V. Cytochrome P450 and liver diseases. *Curr Drug Metab.* 2004;5:273–282.
31. Bastien MC, Leblond F, Pichette V, et al. Differential alteration of cytochrome P450 isoenzymes in two experimental models of cirrhosis. *Can J Physiol Pharmacol.* 2000;78:912–919.
32. Peterson TC, Hodgson P, Fernandez-Salguero P, et al. Hepatic fibrosis and cytochrome P450: experimental models of fibrosis compared to AHR knockout mice. *Hepatol Res.* 2000;17:112–125.
33. Abel S, Davis JD, Ridgway CE, et al. Pharmacokinetics, safety and tolerability of a single oral dose of maraviroc in HIV-negative subjects with mild and moderate hepatic impairment. *Antivir Ther.* 2009;14:831–837.