HIV SPECIALTY PHARMACY RESIDENCY RESEARCH PROJECT

THE EFFECTS OF THE DIRECT ACTING ANTIVIRAL AGENT BOCEPREVIR ON THE PHARMACOKINETICS OF MARAVIROC IN HEALTHY VOLUNTEERS

Dominic Martel[1,2], Nancy Sheehan[2,3], Cécile Tremblay[4], Jacques Turgeon[3,5], Alice Tseng[1,6], Grégoire Noël[4], Denis Phaneuf[4], Denis Thibeault[7], Line Labbé[3]

1- Immunodeficiency clinic, Toronto General Hospital, University Health Network
2- Chronic Viral Illness Service, Montreal Chest Institute, McGill University Health Centre (MUHC)
3- Faculté de pharmacie, Université de Montréal
4- Unité hospitalière de recherche, d'enseignement et de soins sur le SIDA, Hôtel-Dieu, Centre hospitalier de l'Université de Montréal (CHUM)
5- Centre de recherche du CHUM
6- Leslie Dan Faculty of Pharmacy, University of Toronto
7- Royal Victoria Hospital, MUHC

March 2013

Table of contents

Acknowledgments

The HIV specialty pharmacy resident wishes to acknowledge many persons without whom his research project would have never been possible. First, many thanks to the program and project coordinators, Dr. Alice Tseng and Nancy Sheehan, for all the support and feedback provided during the study and the residency, especially Nancy in providing the study idea and design at the beginning of the year. Nancy Sheehan acted as a tremendous preceptor for the whole study and was key and essential in the long and hazardous process of study design, submission to ethics, clinical trial application and study coordination. Many thanks to Dr. Line Labbé for providing research funding without which the project idea would have never grew. Dr. Labbé was also available for valuable feedback and was key to the study design and coordination. Many thanks to Dr. Jacques Turgeon for providing laboratory and office space as well as to François Bélanger, his research associate, for providing administrative support in the research account management at the study site. The resident would also like to recognize Karina Chahinian's work, a pharmacy student, who helped to coordinate the study and recruit study participants. Many thanks to Dr. Cécile Tremblay who offered her expertise as the study site principal investigator and for physical examination of the study participants. Dr. Tremblay also provided guidance to the resident at the study site in the research process and was kind enough to provide nursing staff for blood work and vital signs measurement. Many thanks to Dr. Denis Phaneuf and Dr. Grégoire Noël for the physical examination of study participants. Stéphanie Matte and Pascale Arlotto, registered nurses, need to be thanked for their availability and guidance at the study site. The resident also wishes to acknowledge Jade Huguet, a PhD student from Dr. Jacques Turgeon's laboratory, who shared with the resident her past experience in the process of a clinical trial in healthy volunteers. The resident also wishes to thank Tudor Luncean, assistant nurse, for blood work and study coordination during the pharmacokinetic days. Many thanks to Mélanie Pérusse at PharmaNet allowing the resident to borrow special catheters (Vasofix®). The resident also wishes to thank Marie-Josée Samson, Louise Ares and Francine Courville at the Centre de Recherche du Centre hospitalier de l'Université de

Montréal for local research study guidance, procedures and clerical support. Finally, the study team wants to acknowledge the study volunteers without whom the research project would have never been possible.

Important Note

The following report is required for the completion of the HIV Specialty Pharmacy Residency Program. However, the reader is advised that the study has not yet been completed and that it contains preliminary data. The project summarizes the work completed to December 2012, but as of February 2013, preliminary analysis from five patients was available and this information was inserted for completeness (Abstract, Table 2, Figure 2). The results and discussion section were made in the expectation that boceprevir would influence the pharmacokinetics of maraviroc. This was done for academic purposes. Therefore, conclusions need to be interpreted with caution.

Abstract

Background: Boceprevir is a direct acting antiviral agent used in the treatment of hepatitis C (HCV). Its clinical efficacy is being investigated in patients co-infected with HIV and HCV. Boceprevir displays many drug-drug interactions with various medications including antiretrovirals, where it has been shown to increase or decrease CYP3A4/5 substrates. It is also a weak inhibitor of P-glycoprotein. No data are yet available on the use of this agent in combination with maraviroc, a CCR5 antagonist which is a substrate of CYP3A4 and of P-glycoprotein.

Materials and Methods: This pharmacokinetic (PK) phase 1, single center, open-label, crossover single-sequence drug-drug interaction study was conducted in healthy Caucasian males. Subjects were selected according to a strict protocol based on physical examination and laboratory tests. Subjects received maraviroc 150 mg every 12 hours for 5 days followed by co-administration of maraviroc 150 mg every 12 hours with boceprevir 800 mg every 8 hours with food for 14 days. On days 5 and 19, maraviroc plasma concentrations were determined by high performance liquid chromatography coupled to a tandem mass spectrometer before and at 0.5, 1, 1.5, 2, 4, 6, 8 and 12 hours after the morning maraviroc dose. Geometric mean ratios (GMR) of AUC_{0-12} (area under the concentration-time curve for the 12 hours dosing interval), C_{max} (maximum concentration) and C_{tau} (concentration at the end of the dosing interval) were calculated. From these data, lack of interaction was concluded if the 90% confidence interval of the GMR (test/reference) fell completely within 80-125%. Individual maraviroc pharmacokinetic parameters were calculated using non-compartmental analysis (WinNonlin 6.3, Pharsight). Information regarding adverse events (AEs) was collected throughout the study and up to 7 days after the end of the study.

Results: As of January 2013, a total of 15 male participants consented to the study and 5 subjects were enrolled and completed the study (median age: 25 years; median weight: 79.6 kg; median body mass index: 24.6 kg/m^2). Boceprevir significantly increased the exposure of maraviroc with AUC_{0-12} GMR [90% confidence interval] of 2.28 [1.24-3.32]

and C_{tau} GMR of 3.62 [2.64-4.60]. Boceprevir did not significantly change maraviroc C_{max} (GMR of 1.25 [0.16-2.34]). Maraviroc exposures with boceprevir were lower than historical data of maraviroc 300 mg BID without CYP3A4 inhibitors and interindividual variability was high in both treatment arms (mean [%CV]; maraviroc: AUC_{0-12} 0.367 mg*h/L [58%], C_{max} 0.170 mg/L [70%] and C_{tau} 0.007 mg/L [52%]; maraviroc+boceprevir: AUC_{0-12} 0.923 mg*h/L [69%], C_{max} 0.212 mg/L [62%] and C_{tau} 0.030 mg/L [69%]). Overall, the study drugs were very well tolerated and AEs reported were mild to moderate (overall incidence 80%; n=4/5). The most common AE was dysgeusia (80%), a known side effect of boceprevir. No grade 3 or 4 AEs or laboratory abnormalities were observed.

Conclusions: Co-administration of boceprevir and maraviroc resulted in significantly enhanced exposure of maraviroc. Our results suggest that boceprevir is inhibiting maraviroc's CYP3A4-mediated metabolism and/or P-glycoprotein. Given the magnitude of the interaction, maraviroc 150 mg every 12 hours is recommended when used with boceprevir.

Introduction

Co-infection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is frequent because of shared modes of viral transmission. Between 20 and 30% of HIV-infected patients are also infected with HCV (1-3). More than 33 million people live with HIV worldwide (4). In contrast, HCV infection is more prevalent as it affects more than 170 million people around the globe, being a leading cause of chronic hepatitis, cirrhosis, liver cancer and the most important indication for liver transplantation (5).

Despite the decrease in mortality and morbidity in HIV-infected individuals since the introduction of potent combination antiretroviral therapy (cART), HCV-related end-stage liver disease (ESLD) now represents a leading cause of death in these patients (6, 7). Progression to cirrhosis is two to threefold higher in co-infected patients than HCV mono-infected patients (8 , 9).

The goal of anti-HCV therapy is to increase long-term survival of infected patients with the hope of achieving sustained virologic response (SVR), that is a level of serum HCV RNA that is undetectable 24 weeks after the end of therapy. Treatment of chronic HCV in HIV co-infected patients is crucial because of the risk to more rapid progression to ESLD and a greater risk of hepatotoxicity to antiretroviral therapy (ART) (10, 11).

The recent introduction of boceprevir and telaprevir, two direct acting antiviral agents (DAAs) against HCV, changed the standard of care for the treatment of chronic HCV infection with genotype 1 to triple therapy containing a DAA in combination with pegylated (PEG) interferon (IFN)-alpha/ribavirin in HCV mono-infected treatment naïve and experienced patients (12). More specifically with regards to boceprevir in combination with PEG IFN-alpha/ribavirin in treatment-naïve and experienced patients, sustained virologic response (SVR) rates reached levels as high as 70% in clinical studies (13, 14).

The use of boceprevir in HIV/HCV co-infection is also of growing interest and supported by recent data. An interim analysis of a randomized double-blind placebo-controlled study of boceprevir/PEG IFN-alpha/ribavirin in HCV treatment naïve HCV/HIV co-infected patients showed that 63.9% of patients on boceprevir/PEG IFN-alpha/ribavirin had an undetectable HCV RNA at 48 weeks as compared to 29.4% of patients on PEG IFN-alpha/ribavirin. In addition, preliminary safety data in co-infected patients showed a profile consistent with the use of boceprevir in HCV mono-infected patients with no change in $CD4^+$ counts and HIV viral load. Of interest, all patients were on ART with most patients being on protease inhibitors (15).

Boceprevir is a novel HCV NS3/4A serine protease inhibitor (PI). Boceprevir metabolism is complex with great potential for drug-drug interactions. Boceprevir is metabolized by aldo-keto reductases (AKR1C2 and AKR1C3), but also through CYP3A4 and CYP3A5 microsomal enzymes (16-18). Boceprevir is also a substrate and a weak inhibitor of P-glycoprotein (P-gp) and is an *in vitro* inhibitor of OATP1B1 hepatocyte transporters and BCRP gut transporters (18-21). In addition, boceprevir is a strong inhibitor of CYP3A4/3A5 and drugs metabolized by this pathway may have increased exposure when administered with this product (18). Indeed, boceprevir is known to significantly increase midazolam, atorvastatin, cyclosporine and tacrolimus exposures (all CYP3A4 substrates) *in vivo* and this may have profound clinical consequences (18, 22, 23). *In vitro* data have shown that boceprevir does not induce CYP3A4/5 (18).

Many studies have investigated the drug-drug interaction potential of boceprevir with antiretrovirals. Boceprevir increases the C_{max} and the area under the curve (AUC) of efavirenz (efavirenz C_{max} ↑ 11 % and AUC ↑ 20 %), while boceprevir C_{max} and AUC are decreased when administered with ritonavir (boceprevir C_{max} ↓ 27% and AUC ↓ 19 %) and efavirenz (boceprevir C_{max} ↓ 8 % and AUC ↓ 19 %), respectively *in vivo* (18, 24). Surprisingly, a study has revealed that boceprevir decreases the minimum concentration (C_{min}) of atazanavir, lopinavir and darunavir (all CYP3A4 substrates) by 49, 43 and 59%, respectively. The AUCs of these HIV protease inhibitors were decreased by 34 to 44% (25). These data suggest that boceprevir displays unexpected *in vivo* interactions.

Contradictory *in vitro* and *in vivo* drug interaction study results are not uncommon. Furthermore, lopinavir/ritonavir and darunavir/ritonavir decreased boceprevir AUC by 45 and 32%, respectively (25). These results are not surprising as ritonavir and lopinavir are known CYP3A4 inducers (26). An unexpected drug interaction was also observed with etravirine (etravirine AUC decreased by 23% and C_{min} decreased by 29%) (27). On the other hand, raltegravir does not appear to interact *in vivo* with boceprevir (28).

Because of these complex drug-drug interactions, antiretroviral alternatives such as maraviroc may need to be considered for the treatment of HIV/HCV co-infected patients. Maraviroc inhibits the binding of HIV-1 gp120 to CCR5, therefore preventing the entry of HIV across the human cell membrane (29). The efficacy of maraviroc is dependent on the patient being infected with a CCR5-tropic virus. Maraviroc was shown to be effective in both treatment-naïve and treatment-experienced HIV patients (30-32).

Maraviroc is usually given as 300 mg twice daily with or without food but the dose may change depending on the patient's concomitant medication. Maraviroc does not inhibit any of the major CYP450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). Maraviroc's major metabolic routes are oxidation and N-dealkylation and *in vitro* studies demonstrated that maraviroc is primarily metabolized by CYP3A4 (33-35). Maraviroc is also a substrate of P-gp (34, 35). Concomitant use of maraviroc with known CYP3A4 inhibitors (ketoconazole, itraconazole, delavirdine, clarithromycin, HIV PIs except tipranavir/ritonavir) requires maraviroc dosage to be reduced to 150 mg twice a day while its use with CYP3A4 inducers (efavirenz, etravirine, rifampin, carbamazepine, phenobarbital, phenytoin) necessitates maraviroc to be used at 600 mg twice daily (34, 35).

Given the similar metabolic routes taken by maraviroc and boceprevir, that is CYP3A4, it is predicted that these molecules will interact. Therefore, a phase I pharmacokinetic drug-drug interaction study in healthy volunteers was conducted. Furthermore, evaluation of this potential interaction is warranted to propose adequate dosing recommendations for maraviroc when given with boceprevir.

Methodology

Study design

This phase 1, single center, open-label, crossover single-sequence drug-drug interaction study in healthy Caucasian males was begun in July 2012, and includes data from participants recruited to Decembrer 3rd 2012 at the Centre hospitalier de l'Université de Montréal (CHUM), Montréal, Québec, Canada. The primary objective of the study was to evaluate the effects of boceprevir on the pharmacokinetics of maraviroc in healthy volunteers. The secondary objective was to determine the appropriate maraviroc dose to be taken when given concomitantly with boceprevir.

Healthy volunteers received maraviroc (Celsentri, ViiV Healthcare) 150 mg every 12 hours from day 1 to 5 followed by maraviroc 150 mg every 12 hours with boceprevir (Victrelis, Merck) 800 mg every 8 hours with food from days 5 to 19. Twelve hour intensive pharmacokinetic (PK) days were scheduled on days 5 and 19 (Figure 1). Maraviroc's steady-state terminal elimination half-life is between 14 to 18 hours (35) and thus maraviroc is expected to be at steady-state after 4 days of administration. Boceprevir's mean elimination half-life is 3 hours (18). As such, steady-state conditions are expected after the first day of administration. Nevertheless, a treatment duration of 14 days was chosen as optimal steady-state conditions to account for potential induction effects of boceprevir on metabolic enzymes and/or drug transporters. On PK days, morning maraviroc and boceprevir doses were administered with a standardized breakfast (490 kcal, 16,6 g of lipids) and the afternoon boceprevir dose was administered with a standardized snack (284 kcal, 10 g of lipids).

Adherence assessment was done by the investigators on days 5 and 19 by counting remaining medication and participants were asked to fill a diary to indicate the date and time of each dose intake. The diary was reviewed with the participant on study visits on days 5 and 19.

Study participants

Healthy Caucasian males, aged 18-50 years old, non-smokers, drinking less than 14 units of alcohol per week, with a body mass index (BMI) 18.0-30.0 kg/m^2 were included in the study. The study population was limited to Caucasian males to minimize interpatient pharmacokinetic variability. Participants underwent history/physical examination, laboratory evaluations (biochemical, hematological, urinalysis) and electrocardiogram prior to study entry. Participants needed to have systolic blood pressure between 105 and 130 mmHg, diastolic blood pressure between 60 and 90 mmHg, supine heart rate between 60 and 100 beats per minute, LDL-cholesterol ≤ 5 mmol/L, triglycerides ≤ 1.7 mmol/L and a 10 year estimate of cardiovascular (CV) disease risk of ≤ 10% ("low risk") as per the Framingham risk score modified for family history (doubling of CV risk if any CV disease in a first-degree relative before 60 years of age); the modified Framingham risk score takes into account age, HDL-cholesterol, total cholesterol, systolic blood pressure, smoker status, presence of diabetes and family history of CV disease (36). Exclusion criteria included positive HIV (ELISA test and Western Blot), hepatitis B (HBsAg positive or HBsAg negative with positive anti-HBcAg and negative anti-HBsAg) or hepatitis C (anti-HCV serology) test result at screening, a positive illicit drug test or the use of intravenous drugs in the last 6 months and a history of postural hypotension, cardiac disease, kidney or liver impairment. Subjects with unprotected sexual activities during the last 6 months with a new or recent partner were also excluded. Participants who received any experimental medication within the last 2 months and/or donated blood during the previous 2 months or who intended to donate blood within 2 months following completion of the study were also not allowed in the study. Prescription drugs, over the counter drugs, recreational drugs, herbal or dietary supplements including vitamins and grapefruit juice were not allowed within 15 days of study initiation (day 1) except for acetaminophen and/or ibuprofen on an as needed basis. These products were also prohibited during the study (except for as needed acetaminophen and/or ibuprofen). Volunteers were all able to understand and comply with the protocol requirements and all signed the informed consent form prior to any study procedure. Subjects with a social condition, psychological or addictive disorder that

would impair protocol adherence were excluded from the study. Finally, participants were asked to use an effective barrier method of contraception during the study.

Pharmacokinetic sampling

On PK days (days 5 and 19), the morning maraviroc was taken at the study site and blood samples were collected pre morning maraviroc dose (0), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours after the maraviroc dose. Blood samples (5-6 mL each) were collected in tubes containing sodium heparin, centrifuged for 5 minutes (3000 g), and the collected plasma was stored in labeled polypropylene tubes at $\leq$ -40^{o}C within 4 hours of blood collection.

Maraviroc analytical methods

Plasma concentrations of maraviroc were measured using a high performance liquid chromatography system (Shimadzu Prominence system from Mandel, Guelph, Ontario, Canada) coupled to a tandem mass spectrometer (API 4000Q trap from AB Sciex, Concord, Ontario, Canada) at the Royal Victoria Hospital of the McGill University Health Centre. Measures were done with the isotopic dilution technique with an ESI source in positive mode. The maraviroc analytical methods were already developed at this laboratory. The laboratory participates in two international external quality control programs (KKGT in the Netherlands and Asqualab in France). The intra-assay and inter-assay coefficients of variation for maraviroc are respectively 0.8-5% and 3.4-5%. The lower limit of quantification (LLOQ) for maraviroc is 0.01 mg/L.

Sample size

A sample size of 9 healthy volunteers was determined to be sufficient to detect a 40% difference in mean AUC of maraviroc with boceprevir versus maraviroc alone with a power of 80% and a type 1 error of 5% (two-sided) based on the assumptions that the

mean AUC of maraviroc is 2908 ng*h/mL and the standard deviation is 727 ng*h/mL (intra-patient coefficient of variation %CV of 25%) (Pfizer data on file). Considering historical interaction data between boceprevir and other CYP3A4 substrates (in the absence of ritonavir), the 40% difference in mean AUC chosen to calculate the sample size was conservative to ensure sufficient sample size (18, 22, 23). Assuming a maximum dropout rate of 20%, 11 patients were enrolled in the study in order to obtain a final sample size of at least 9 individuals.

Pharmacokinetics and statistical analyses

Pharmacokinetics parameters of maraviroc were estimated by the application of a nonlinear curve-fitting software (WinNonlin) using noncompartmental methods and including maximum plasma concentration (C_{max}), time to reach the maximum concentration (T_{max}), the area under the plasma concentration-time curve for the 12 hours dosing interval (AUC_{0-12}), elimination half-life ($t_{1/2}$), oral clearance (CL/F), volume of distribution (V_D) and concentration at the end of the dosing interval (C_{tau}). The elimination rate constant (k_{el}) was calculated by an analysis using least squares linear regression of at least 3 data points in the elimination phase. The $t_{1/2}$ was calculated as $t_{1/2} = \ln 2/k_{el}$. The AUC_{0-12} was estimated using the linear trapezoidal rule. The CL/F was calculated as $CL/F = Dose/AUC_{0-12}$. The V_D was calculated as $V_D = Dose/(AUC_{0-12}*k_{el})$.

Natural log transformed geometric means of AUC_{0-12}, C_{max}, and C_{tau} were analyzed. From these data, lack of interaction of the test to reference treatment for maraviroc pharmacokinetics parameters was concluded if 90% confidence interval of the geometric mean ratio (test/reference) fell completely within 80-125% (37). Statistical analyses were conducted using the SPSS software.

Population pharmacokinetic and statistical analyses

The population pharmacokinetic analysis was performed with NONMEM (Nonlinear Mixed Effect Model) computer program. The analysis used mixed-effects regression (fixed and random) to estimate means and variances of the pharmacokinetic parameters of maraviroc and to identify factors that influence them, including co-administration of boceprevir. First, one- and two-compartment models with first-order absorption for the gastrointestinal tract were fitted to the maraviroc data. The estimated pharmacokinetic parameters were the constant of absorption (Ka), the apparent clearance (CL/F), and the volume of distribution (V/F), where F is oral bioavailability. Other pharmacokinetic parameters of maraviroc were derived from the final model, namely, area under the curve (AUC), elimination half life ($t_{1/2}$), maximum plasma drug concentration (Cmax), and time to reach the Cmax according to classical steady-state formulae for repeated oral dosing. Exponential errors following a log-normal distribution were assumed for the description of interpatient variability of the pharmacokinetic parameters. Additive, proportional, and combined additive and proportional models were tested for the intrapatient (random) variability. Potential influencing covariates (especially, co-administration with boceprevir) were incorporated into the structural model. The merit of a more complex model (larger – more parameters) over a less complex sub-model was tested using a "log likelihood-ratio" test: Δobj, the difference of NONMEM objective functions (approximately minus twice the maximized log-likelihood of the data) at convergence for the two models, is referenced to its asymptotic chi-square distribution (df = difference in number of free parameters). The difference was declared significant when $p < 0.05$.

If boceprevir has a significant effect on maraviroc pharmacokinetic, simulations will be performed to determine which dosing regimen of maraviroc should be used during co-administration with boceprevir.

Safety

Patients were seen at the screening visit and on days 1, 5 and 19 and were submitted to a physical exam and a series of test (biochemical, hematological, electrocardiogram) to assess safety of the study drugs. Information regarding adverse events (AE) was collected and recorded throughout the study and up to 7 days after the end of the study. Adverse events were graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (2004) (38).

Study procedures

This trial was approved by the research ethics board of the *Centre de recherche du Centre Hospitalier de l'Université de Montréal* (CHUM) and by the University of Toronto Faculty of Pharmacy Undergraduate Research Ethics Review Committee (FERC), in accordance with the HIV Residency Program Guidelines.

The study was conducted according to the principles of the Declaration of Helsinki, Good Clinical Practice guidelines and local rules and regulations. All subjects signed an informed consent form before any study procedure.

Results

Study subjects

As of December 2012, a total of 15 participants signed the consent form, 5 subjects were enrolled while 3 took the study drugs and completed PK evaluation. A total of 9 participants were excluded from the study based on inclusion/exclusion criteria: bradycardia (n=3), low blood pressure (n=1), liver disease (n=1), excessive alcohol consumption (n=1), unprotected sexual activities in the last 6 months (n=1), positive urine drug screen (n=1) and protocol deviation (n=1). No subject discontinued the study due to an adverse event related to the study drug. Two participants are currently completing the PK study phase and the investigators require 6 more subjects to be enrolled for study completion. One subject is currently in the screening process. A summary of study participants' characteristics is depicted in Table 1.

Maraviroc Pharmacokinetics

Table 2 and Figure 2 summarize the pharmacokinetics of maraviroc given alone compared to the pharmacokinetics of maraviroc when given in combination with boceprevir. Geometric mean ratios for boceprevir AUC, C_{max} and C_{tau} in the presence versus in the absence of boceprevir will be calculated. Changes in maraviroc pharmacokinetic parameters of T_{max}, $t_{1/2}$, CL/F and V_D in the presence compared to absence of boceprevir will also be calculated. Importantly, the lower/higher bound of the 90% confidence interval of the geometric mean ratio (maraviroc+boceprevir/maraviroc) of AUC_{0-12}, C_{max}, and C_{tau} will be compared to the 80-125% no effect boundary in order to determine if the pharmacokinetic of maraviroc is significantly affected by boceprevir and therefore if maraviroc concentration is bioequivalent when administered alone versus in concomitance with boceprevir. Participant adherence to study drugs was excellent, all 3 participants who completed the study showed 100% adherence as observed by pill count and medication diary review.

Maraviroc Population Pharmacokinetics

This section will be completed with the help of Dr Line Labbé once results are available and will allow determination of the proper maraviroc dose to be used when given with boceprevir based on model simulations.

Safety

Clinical and laboratory adverse events noted in the study (n=11) were mild in nature (grade 1). The most common adverse event seen in the study was dysgeusia, a known side-effect of boceprevir which happened in 1/3 (33.3%) individuals during the first maraviroc-only sequence while 3/3 (100%) participants experienced altered taste during the second maraviroc and boceprevir combination sequence. Adverse effects observed at a frequency of more than 10% were headache seen in 1/3 (33.3%) subjects receiving maraviroc alone, and increased appetite, thrombocytopenia and QTc interval prolongation observed each in 1/3 (33.3%) participants on maraviroc and boceprevir combination therapy. The observed QTc prolongation on co-administration of boceprevir and maraviroc was mild (grade 1) and ECG findings showed an increase of the QTc from 430 ms to 457 ms. The thrombocytopenia observed in one participant on co-administration of boceprevir and maraviroc was also mild (grade 1) with platelets decreasing from 145 x 10^9 cells/L to 109 x 10^9 cells/L. Most importantly, no participant stopped study drugs because of adverse reactions. Of note, 1/3 (33.3%) participant experienced a general malaise including fatigue and headache (flu-like syndrome without fever) within a week after discontinuation of study drugs.

Discussion

This study aims to quantify the impact of boceprevir on the pharmacokinetics of maraviroc in HIV negative, HCV negative healthy volunteers. In addition, our study suggests that boceprevir administration with maraviroc is safe as no serious adverse events were observed in study volunteers.

The drug-drug interaction occurring between maraviroc and boceprevir is most probably explained at the level of drug metabolism. Maraviroc is a substrate of CYP3A4 while boceprevir is a known inhibitor of this cytochrome (18, 33-35). Therefore, a change in the exposure of maraviroc is most probably explained by inhibition of CYP3A4 by boceprevir. Drug absorption can also partly explain the change in maraviroc exposure with co-administration of boceprevir as maraviroc is a substrate of P-gp (34, 35) while boceprevir is also known as a substrate of the P-gp drug efflux transporter. The impact of P-gp on the observed interaction may be minor as recent data with digoxin suggests that boceprevir has weak *in vivo* P-gp inhibitory potential (39). Therefore, it is unlikely that the change in maraviroc pharmacokinetics by boceprevir is solely a result of P-gp inhibition by boceprevir. In addition, maraviroc has not been identified as an inhibitor of P-gp *in vivo* (40). Other drug transporters could also be involved in the drug transport process *in vivo*. Boceprevir has been shown to act as an *in vitro* inhibitor of OATP1B1 hepatocyte transporters and BCRP gut transporters (18, 20, 21) while maraviroc has also been implicated as a potential activator of MRP-2 transport (41) or as a substrate for OATP1B1 (42). Nevertheless maraviroc is not thought to clinically depend on the use of these specific transporters and *in vitro* data suggest that drug transporters (except P-gp) are less likely to impact maraviroc interactions with other drugs (41). Thus, it is difficult to predict the real impact of these transporters and other unknown routes of metabolism in explaining the drug interaction between boceprevir and maraviroc.

Because the influence of maraviroc on the pharmacokinetics of boceprevir was considered unlikely, we chose to limit drug exposure in our healthy volunteers and hence

did not measure the drug concentration of boceprevir. However, this is a major limitation of our study as some studies have shown unpredictable two way drug interactions not only with boceprevir (23), but also with maraviroc. Studies in healthy volunteers have shown that maraviroc can decrease overall exposure of amprenavir (43, 44) (effect varies depending on the study, dosing scheme and presence of ritonavir), but the clinical significance of the interaction remains undetermined. Maraviroc was also found to decrease raltegravir AUC and C_{max} by 37% and 33%, respectively (45). This interaction was nevertheless found to be clinically not significant and has not been observed in the clinical setting (45, 46). Despite these results, the impact of maraviroc on the pharmacokinetics of other molecules is thought to be negligible and thus the likelihood that maraviroc will affect boceprevir is low. Finally, our study was conducted in HIV and HCV negative individuals and the applicability of our findings to HIV and HCV infected patients is unclear.

Most reassuring, exposure to maraviroc when given as 150 mg every 12 hours with boceprevir was similar to historical controls when maraviroc was given as 300 mg twice daily or when given 150 mg twice daily with CYP3A4 inhibitors (35). In addition, all patients had maraviroc minimum concentrations above 0.05 mg/L, the proposed target in HIV-1 infected treatment-experienced patients (35, 47, 48).

Many studies have documented potential drug-drug interactions between boceprevir and antiretrovirals. Boceprevir should not be used with efavirenz due to a decrease in AUC and C_{min} of boceprevir of 19% and 44% respectively (24) and the use of boceprevir with HIV PIs (ritonavir-boosted atazanavir, darunavir and lopinavir) is not recommended by the drug company due to two-way negative drug-drug interactions. Indeed, boceprevir decreases C_{min} of atazanavir, lopinavir and darunavir by 49%, 43% and 59%, respectively, while the AUCs of these HIV protease inhibitors were decreased by 34% to 44% (25). Furthermore, lopinavir/ritonavir and darunavir/ritonavir decreased boceprevir AUC by 45% and 32%, respectively (25). An unexpected drug interaction was also observed with etravirine (etravirine AUC decreased by 23% and C_{min} decreased by 29%) (27). A previous study in healthy volunteers has shown that raltegravir can also be

recommended for combined HIV/HCV treatment that include boceprevir due to lack of a clinically significant drug-drug interaction (28).

We anticipate that our results will suggest that maraviroc could be used safely in combination with the DAA boceprevir with proper dosing adjustment. In addition, maraviroc may have additional benefits for HIV/HCV co-infected patients on treatment. Recent data suggest that adding maraviroc to an atazanavir-ritonavir plus tenofovir-emtricitabine regimen in HIV/HCV-co-infected patients naïve to anti-HCV therapy decreases liver fibrosis (49). Although these results are still preliminary, they may point out a beneficial role of maraviroc in this population by reducing liver stiffness. These results are supported by some data indicating that stellate cells in the liver express CCR5 and that this receptor is strongly upregulated in mouse models of liver fibrosis (50, 51). The administration of anti-CCR5 antibodies decreased liver inflammation in mouse models of liver failure (52). CCR5 has been thought to participate in the recruitment of T lymphocytes to the liver in response to HCV chronic infection (53). One study pointed out less severe inflammation and more chances of clearing the HCV infection in women heterozygous for CCR5Δ32 mutation, which prevents the functional expression of the CCR5 receptor (54). Despite these results, a meta-analysis failed to demonstrate a link between susceptibility to HCV infection and the CCR5Δ32 mutation (55). Although the precise role of maraviroc in HCV chronic infection is yet to be proven, it is already indicated for the treatment of HIV infection, and therefore the use of maraviroc in HIV-HCV co-infected patients is of current interest.

Although co-administration of maraviroc and boceprevir was found to be safe as only grade 1 adverse events were observed, one individual displayed a prolongation of the QTc interval when the 2 drugs were administered together. Boceprevir does not increase the QTc interval (18). No QTc prolongation is usually seen when maraviroc is administered at recommended doses, however QTc prolongation was seen in animal models receiving 12 times human doses (35, 56). It is unclear why the participant showed QTc prolongation, but this observation may suggest enhanced maraviroc exposure (to be

confirmed when maraviroc levels become available). The clinical significance of this observation remains unknown at present time.

Suggestions for future research

The therapeutic arsenal against HCV will grow in the next few years, offering tremendous opportunities for investigating potential DDIs between DAAs and other drugs including antiretrovirals. An ongoing study by Pfizer will provide new insights on the influence of the other commercially available HCV PI telaprevir on the pharmacokinetics of maraviroc and on the influence of maraviroc on boceprevir and telaprevir PK. It will be interesting to see if the impact of telaprevir on the pharmacokinetics of maraviroc is of the same amplitude as is the impact of boceprevir on the pharmacokinetics of maraviroc. Indeed, boceprevir is less susceptible than telaprevir to metabolic drug interactions due to multiple metabolic pathways. In addition, telaprevir appears to be a more potent inhibitor/inducer of CYP3A metabolism than boceprevir. For instance, boceprevir increased the AUC and C_{max} of single-dose tacrolimus 0.5 mg (a CYP3A4 substrate) by 17-fold and 9.9-fold whereas telaprevir increased the AUC of single-dose tacrolimus 0.5 mg by 170-fold (23, 57). *In vitro* data have also shown that boceprevir does not induce CYP3A4/5 (18) whereas telaprevir has low *in vitro* potential to induce CYP2C, 3A or 1A (58).

In addition, cohort studies are needed to evaluate the effects of managing drug-drug interactions in the treatment of HCV/HIV co-infected patients. Indeed, most drug-drug interaction studies are done in healthy volunteers, but no clinical data are yet available to determine if the choice of any cART is beneficial in patients on boceprevir or telaprevir. Indeed, retrospective or prospective cohort studies analyzing HCV sustained virologic responses as well as HIV treatment outcomes and antiretroviral exposure may help determine if observed drug-drug interactions between antiretrovirals and DAAs have a real clinical impact on treatment responses. It is also unclear if the decrease in plasma concentrations of boceprevir observed in DDIs studies is even relevant clinically due to the absence of an exposure-response relationship between boceprevir trough or AUC with antiviral activity within the hepatocytes (19). Comparison of non-nucleoside reverse transcriptase (NNRTI), PI, raltegravir and maraviroc based cART may help answering these important questions. In addition, pharmacokinetics studies in HCV/HIV co-infected

patients receiving HCV and HIV antivirals is needed to confirm the drug-drug interactions observed in healthy volunteers. Finally, since adding maraviroc to cART in HIV/HCV-co-infected patients naïve to anti-HCV therapy decreases liver fibrosis (49), it will be interesting to see what is the impact of maraviroc-based regimens on liver disease and markers of cirrhosis including liver stiffness in co-infected patients given potent anti-HCV therapy.

Barriers to project completion

Despite intensive work efforts, it was impossible to complete the project during the HIV specialty pharmacy residency one-year time frame. Many obstacles were faced during the research project and this explains why one year was insufficient to complete this pharmacokinetic phase I drug-drug interaction study.

Research proposal and submission to the research ethics board

Initially, the research proposal was planned to be approved by the ethics research board in March 2012. However, the process took much longer, since the project required a No Objection Letter (NOL) from Health Canada before being submitted to the ethics research board of the CHUM. This document is issued by Health Canada within the review period if the Clinical Trial Application (CTA) is acceptable. Therefore, a CTA had to be prepared and submitted to Health Canada. The process was lengthy and the resident wishes to thank Nancy Sheehan for preparing and submitting the documents to Health Canada. Due to this regulatory delay, the research ethics board only approved the project in July 2012.

Study recruitment and research coordination

A pharmacy summer student, Karina Chahinian, was hired by Dr. Line Labbé to help in the recruitment of study participants from May to August 2012. However, since recruitment could only begin once the research ethics board had approved the project, the student was only available for 2 months. The resident was given office space, telephone and access to OACIS (electronic patient file). Nevertheless, the resident had to lead and organize all the research procedures as no structures or contacts were already set up to conduct a trial of this magnitude. This is something that the resident had not planned ahead. The resident had to initiate contact with the biochemistry/hematology/cardiology/pharmacy/nutrition departments for contract

agreements with the various departments for the cost of tests, analysis and services required by the research protocol. In addition, no research nurse was initially available and the resident had, with the help of the human resources department and Dr. Labbé, find and hire a research nurse. When the study started, the resident discovered that the hired nurse was not a registered nurse, but rather an assistant nurse, which complicated things as available catheters in the CHUM required a registered nurse for patient safety. The assistant nurse required specific catheters that were not available. The resident contacted PharmaNet, a phase I conducting company in Quebec City, in order to borrow special catheters (Vasofix®) that could be used by the assistant nurse while the catheters could be ordered from Germany. In the meanwhile, recruitment of participants was pursued by the pharmacy student and unfortunately was quite unsuccessful. Participants were first recruited via postings at the CHUM, but since the investigators were looking for healthy volunteers, the strategy did not provide a single call since most visitors in the hospital are sick. The resident thought of innovative strategies for publicity such as the Internet, which worked well. Nevertheless, recruitment was difficult and frustrating, about 9/10 interested participants did not show up at given appointments for discussion and signature of the informed consent form. Many participants were also lost to follow-up before initiation of any study procedure. In addition, summer may not be the best time for recruiting participants as many interested participants may be away and/or on vacation. Finally, among participants screened, many were excluded since they did not meet the inclusion criteria and this required more participants to be screened overall. Some of the inclusion/exclusion criteria may have been too strict and should have been modified as some patients were excluded despite being healthy. For instance, healthy participants with a supine heart rate between 50-60 beats per minute, or with a systolic blood pressure between 100 and 135 mmHg should have been considered as adequate candidates, but due to the inclusion/exclusion criteria these participants were excluded.

Availability of physicians and nurses

Prior to study initiation, three physicians agreed to see study patients for physical examinations at screening and on PK days 5 and 19. However, one of the physicians was

only available one day every two weeks while the two other physicians had very little time for research activities. During the study, one physician even stopped seeing patients due to his overwhelming schedule and for misunderstanding of time needed to see study patients. Therefore, in the best scenario, a physician could see one or two patients every week and moments where the patient, the physician, the assistant nurse and the resident were all available together were quite rare. In addition, the study took place in the summer and many workers including physicians at the CHUM were on vacation, therefore complicating the organization of the study. The resident also did not have an available nurse at all time for blood work and was quite fortunate to have help from Stéphanie Matte and Pascale Arlotto, Dr. Tremblay's research nurses, for screening of the patients. Given the complexity of schedules, it was extremely difficult to find days that would fit the schedule of all health professionals, especially for the PK days that needed to be on specific dates. This all slowed down the whole research process. Finally, since the resident had academic rotations to fulfill, he could not be available at all time for recruitment of study participants.

Conclusion and future plans

In summary, the study could not be completed on time due to delays in the submission of the proposal to ethics, difficulty in the recruitment of study participants and the challenge in having physicians available to see patients for physical examination.

The resident will pursue completion of the research project at the CHUM. To overcome the limited availability of the physicians, the resident will find other physicians interested to participate in the screening of the patients and will amend the protocol accordingly. Since half of the participants have been recruited, the study is expected to be completed in the spring of 2013.

References

1. Staples CT, Jr., Rimland D, Dudas D. Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. Clin Infect Dis. 1999 Jul;29(1):150-4.

2. Sherman KE, Rouster SD, Chung RT, Rajicic N. Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. Clin Infect Dis. 2002 Mar 15;34(6):831-7.

3. Amin J, Kaye M, Skidmore S, Pillay D, Cooper DA, Dore GJ. HIV and hepatitis C coinfection within the CAESAR study. HIV Med. 2004 May;5(3):174-9.

4. UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2010. 2010 [October 4, 2011]; Available from: http://www.unaids.org/globalreport/Global_report.htm.

5. Davis GL, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the United States. Liver Transpl. 2003 Apr;9(4):331-8.

6. Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis. 2001 Feb 1;32(3):492-7.

7. Smit C, van den Berg C, Geskus R, Berkhout B, Coutinho R, Prins M. Risk of hepatitis-related mortality increased among hepatitis C virus/HIV-coinfected drug users compared with drug users infected only with hepatitis C virus: a 20-year prospective study. J Acquir Immune Defic Syndr. 2008 Feb 1;47(2):221-5.

8. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001 Aug 15;33(4):562-9.

9. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. AIDS. 2008 Oct 1;22(15):1979-91.

10. Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med. 2006 Aug 14-28;166(15):1632-41.

11. Labarga P, Soriano V, Vispo ME, Pinilla J, Martin-Carbonero L, Castellares C, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. J Infect Dis. 2007 Sep 1;196(5):670-6.

12. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011 Oct;54(4):1433-44.

13. Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206.

14. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1207-17.

15. Sulkowski M, Pol S, Cooper C, Fainboim H, Slim J, Rivero A, et al., editors. Boceprevir + pegylated interferon + ribavirin for the treatment of HCV/HIV co-infected patients: end of treatment (week 48) interim results. 19th Conference on Retroviruses and Opportunistic Infections; March 5-8, 2012; Seattle. Paper #47.

16. Kempf DJ, Klein C, Chen HJ, Klein LL, Yeung C, Randolph JT, et al. Pharmacokinetic enhancement of the hepatitis C virus protease inhibitors VX-950 and SCH 503034 by co-dosing with ritonavir. Antivir Chem Chemother. 2007;18(3):163-7.

17. Ghosal A, Yuan Y, Tong W, Su AD, Gu C, Chowdhury SK, et al. Characterization of human liver enzymes involved in the biotransformation of boceprevir, a hepatitis C virus protease inhibitor. Drug Metab Dispos. 2011 Mar;39(3):510-21.

18. Product Monograph. VICTRELIS. Merck Canada Inc. 2012 [November 18, 2012]; Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/info.do?code=85593&lang=eng.

19. CDER. Boceprevir: clinical pharmacology and biopharmaceutics review. 2011 [December 27, 2012]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202258orig1s000clinpharmr.pdf.

20. Victrelis (boceprevir) FDA briefing document. 2011 [November 18, 2012]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202258Orig1s000ClinPharmR.pdf.

21. Chu X CX, Cui D, Evers R, Green MD, Ghosal A, et al., editor. In vitro assessment of drug-drug interaction potential of boceprevir as an Inhibitor and inducer of drug metabolizing enzymes and transporters 62th Annual Meeting of the American Association for the Study of Liver Diseases November 6-9, 2011; San Francisco. Abstract 378.

22. Hulskotte EGJ GS, Xuan F, van Zutven MGJA, O'Mara E, Galitz L et al., editor. Pharmacokinetic evaluation of the interaction between the hepatitis C virus protease inhibitor boceprevir and the HMG-CoA reductase inhibitors atorvastatin and pravastatin. 16th Annual Meeting of HEP DART; December 4-8, 2011; Koloa, Hawaii, USA. Poster 122.

23. Hulskotte E, Gupta S, Xuan F, van Zutven M, O'Mara E, Feng HP, et al. Pharmacokinetic interaction between the hepatitis C virus protease inhibitor boceprevir and cyclosporine and tacrolimus in healthy volunteers. Hepatology. 2012 Nov;56(5):1622-30.

24. Seden K, Back D. Directly acting antivirals for hepatitis C and antiretrovirals: potential for drug-drug interactions. Curr Opin HIV AIDS. 2011 Nov;6(6):514-26.

25. Hulskotte EG, Feng HP, Xuan F, van Zutven MG, Treitel MA, Hughes EA, et al. Pharmacokinetic Interactions Between the HCV Protease Inhibitor Boceprevir and Ritonavir-Boosted HIV-1 Protease Inhibitors Atazanavir, Darunavir, and Lopinavir. Clin Infect Dis. Nov 15.

26. Product Monograph. Kaletra. AbbVie Corporation. 2012 [November 18, 2012]; Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/info.do?code=77104&lang=eng.

27. Hammond KP, Wolfe P, Burton JR, Jr., Predhomme JA, Ellis CM, Ray ML, et al. Pharmacokinetic Interaction between Boceprevir and Etravirine in HIV/HCV Seronegative Volunteers. J Acquir Immune Defic Syndr. Oct 15.

28. de Kanter CT, Blonk MI, Colbers AP, Schouwenberg BJ, Burger DM. Lack of a Clinically Significant Drug-Drug Interaction in Healthy Volunteers Between the Hepatitis C Virus Protease Inhibitor Boceprevir and the HIV Integrase Inhibitor Raltegravir. Clin Infect Dis. Oct 19.

29. Dorr P, Westby M, Dobbs S, Griffin P, Irvine B, Macartney M, et al. Maraviroc (UK-427,857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity. Antimicrob Agents Chemother. 2005 Nov;49(11):4721-32.

30. Gulick RM, Lalezari J, Goodrich J, Clumeck N, DeJesus E, Horban A, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. N Engl J Med. 2008 Oct 2;359(14):1429-41.

31. Fatkenheuer G, Nelson M, Lazzarin A, Konourina I, Hoepelman AI, Lampiris H, et al. Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection. N Engl J Med. 2008 Oct 2;359(14):1442-55.

32. Cooper DA, Heera J, Goodrich J, Tawadrous M, Saag M, Dejesus E, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the

treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. J Infect Dis. 2010 Mar 15;201(6):803-13.

33. Hyland R, Dickins M, Collins C, Jones H, Jones B. Maraviroc: in vitro assessment of drug-drug interaction potential. Br J Clin Pharmacol. 2008 Oct;66(4):498-507.

34. Abel S, Back DJ, Vourvahis M. Maraviroc: pharmacokinetics and drug interactions. Antivir Ther. 2009;14(5):607-18.

35. Product Monograph. CELSENTRI. ViiV Healthcare ULC. 2012 [November 18, 2012]; Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/info.do?code=78519&lang=eng.

36. Genest J, McPherson R, Frohlich J, Anderson T, Campbell N, Carpentier A, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. Can J Cardiol. 2009 Oct;25(10):567-79.

37. FDA, Department of Health and Human Services. Guidance for Industry-In vivo Drug Metabolism/Drug Interaction Studies-Study Design, Data Analysis, and Recommandations for Dosing and Labeling; FDA: Rockville, MD, USA. 1999:1-16.

38. National Institute of Allergy and Infectious Diseases DoA. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Bethesda, MD: US Department of Health and Human Services. 2004.

39. Jumes P FH, Xuan F et al. Pharmacokinetic interaction between the HCV protease inhibitor boceprevir and digoxin in healthy adult volunteers. 7th International Workshop on Clinical Pharmacology of Hepatitis Therapy; June 2012; Cambridge, USA. Abstract PK_05.

40. Vourvahis M FJ, Choo HW, et al, editor. Lack of a clinically relevant effect of maraviroc on the pharmacokinetics of digoxin in healthy volunteers. 12th International Workshop on Clinical Pharmacology of HIV Therapy; April 13-15th, 2011; Miami, USA. Abstract P_14.

41. Zembruski NC, Buchel G, Jodicke L, Herzog M, Haefeli WE, Weiss J. Potential of novel antiretrovirals to modulate expression and function of drug transporters in vitro. J Antimicrob Chemother. 2011. Apr;66(4):802-12.

42. Siccardi M, D'Avolio A, Nozza S, Simiele M, Baietto L, Stefani FR, 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. Dec;20(12):759-65.

43. Luber A CD, Slowinski PD, et al, editor. Steady-state pharmacokinetics of maraviroc and amprenavir alone and in combination after maraviroc is given BID with unboosted or ritonavir- boosted fosamprenavir once- or twice-daily in fasted healthy volunteers. 10th International Workshop on Clinical Pharmacology of HIV Therapy; April 15-17, 2009; Amsterdam, the Netherlands. abstract P_31.

44. Vourvahis M PA, Mendes da Costa L, et al., editor. Pharmacokinetic interaction between maraviroc and fosamprenavir/ritonavir: an open-label, fixed-sequence study in healthy volunteers. 13th International Workshop on Clinical Pharmacology of HIV Therapy; April 16-18, 2012; Barcelona, Spain. Abstract P_12.

45. Andrews E, Glue P, Fang J, Crownover P, Tressler R, Damle B. Assessment of the pharmacokinetics of co-administered maraviroc and raltegravir. Br J Clin Pharmacol. 2010 Jan;69(1):51-7.

46. Baroncelli S, Villani P, Weimer LE, Ladisa N, Francisci D, Tommasi C, et al. Raltegravir plasma concentrations in treatment-experienced patients receiving salvage regimens based on raltegravir with and without maraviroc coadministration. Ann Pharmacother. 2010 May;44(5):838-43.

47. McFayden L JP, Wade J, et al. Maraviroc exposure response analysis: phase 3 antiviral efficacy in treatmentexperienced HIV+ patients. 16th Population Approach Group in Europe Meeting; June 2007; Kobenhavn, Denmark. Abstract P4-13.

48. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. [December 30, 2012]; Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

49. Nasta P GF, Borghi F, Chiari E, Paderni A, Carosi G., editor. Liver stiffness (LS) change in HIV-Hepatitis C (HCV) coinfected patients treated with CCR5 inhibitor based antiretroviral therapy. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 17-20, 2011; Chicago. Abstract H3-810. .

50. Schwabe RF, Bataller R, Brenner DA. Human hepatic stellate cells express CCR5 and RANTES to induce proliferation and migration. Am J Physiol Gastrointest Liver Physiol. 2003 Nov;285(5):G949-58.

51. Seki E, De Minicis S, Gwak GY, Kluwe J, Inokuchi S, Bursill CA, et al. CCR1 and CCR5 promote hepatic fibrosis in mice. J Clin Invest. 2009 Jul;119(7):1858-70.

52. Murai M, Yoneyama H, Harada A, Yi Z, Vestergaard C, Guo B, et al. Active participation of CCR5(+)CD8(+) T lymphocytes in the pathogenesis of liver injury in graft-versus-host disease. J Clin Invest. 1999 Jul;104(1):49-57.

53. Larrubia JR, Benito-Martinez S, Calvino M, Sanz-de-Villalobos E, Parra-Cid T. Role of chemokines and their receptors in viral persistence and liver damage during chronic hepatitis C virus infection. World J Gastroenterol. 2008 Dec 21;14(47):7149-59.

54. Goulding C, McManus R, Murphy A, MacDonald G, Barrett S, Crowe J, et al. The CCR5-delta32 mutation: impact on disease outcome in individuals with hepatitis C infection from a single source. Gut. 2005 Aug;54(8):1157-61.

55. Wheeler J, McHale M, Jackson V, Penny M. Assessing theoretical risk and benefit suggested by genetic association studies of CCR5: experience in a drug development programme for maraviroc. Antivir Ther. 2007;12(2):233-45.

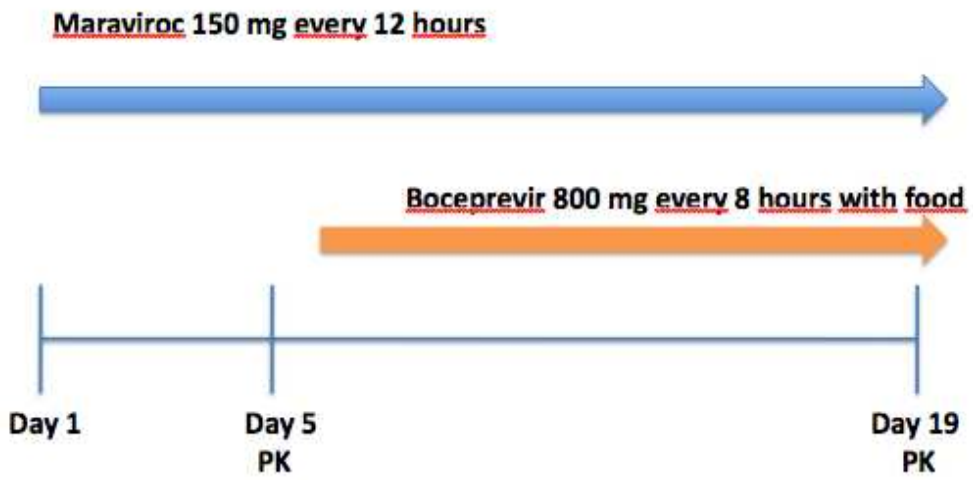
56. Davis JD, Hackman F, Layton G, Higgins T, Sudworth D, Weissgerber G. Effect of single doses of maraviroc on the QT/QTc interval in healthy subjects. Br J Clin Pharmacol. 2008 Apr;65 Suppl 1:68-75.

57. Garg V, van Heeswijk R, Lee JE, Alves K, Nadkarni P, Luo X. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. Hepatology. 2011 Jul;54(1):20-7.

58. Medication guide. INCIVEK. Vertex Pharmaceuticals Inc. 2012 [Decembrer 27, 2012]; Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/dispatch-repartition.do?lang=eng.

Figures and tables

Figure 1. Treatment plan of the study



Days 1 to 5: maraviroc 150 mg (1 tablet) every 12 hours. Day 5: 12 hour intensive pharmacokinetic (PK) day. Days 6 to 19: maraviroc 150 mg (1 tablet) every 12 hours + boceprevir 800 mg (4 capsules of 200 mg) every 8 hours with food. Day 19: 12 hour intensive PK day

Table 1. Summary of study subjects baseline demographics

	Excluded patients (n=9)	Included patients (n=5)
Age (y), median (range)	28 (26-38)	25 (18-41)
Weight (kg), median (range)	73.3 (65.8-93.3)	79.6 (67.7-82.5)
BMI ($kg/m^{2/}$), median (range)	24.3 (18.4-28.5)	24.6 (18.0-27.6)
Males, N (%)	9 (100%)	5 (100%)
Caucasians. N (%)	9 (100%)	5 (100%)

Figure 2. Mean maraviroc (MRV) concentrations (mg/L) alone versus in combination with boceprevir (MRV+BOC) over time (h)

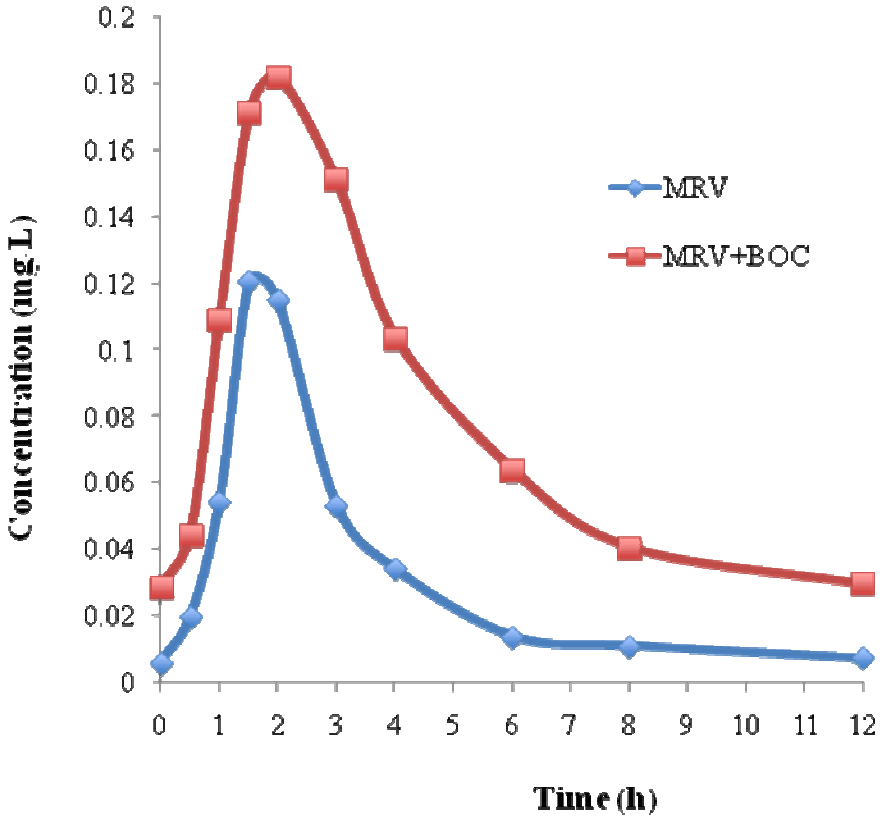


Table 2. Maraviroc pharmacokinetics alone or in combination with boceprevir

	C_{max} (mg/L)	AUC_{0-12} (mg*h/L)	C_{tau} (mg/L)	CL/F (L/h)	V_D/F (L)	$t_{1/2}$* (h)	T_{max}* (h)
MRV	0.170 (70%)	0.367 (58%)	0.007 (52%)	550 (101%)	6162 (91%)	7.80 (4.98-8.68)	1.5 (1-3)
MRV + BOC	0.212 (62%)	0.923 (69%)	0.030 (69%)	262 (90%)	3521 (65%)	4.40 (3.30-8.46)	1.5 (1-2)
GMR (90% CI) MRV + BOC vs. MRV	1.25 (0.16-2.34)	2.28 (1.24-3.32)	3.62 (2.64-4.60)				

MRV: maraviroc; BOC: boceprevir; GMR: geometric mean ratio; CI: confidence interval

*All the data except for T_{max} and $t_{1/2}$ are presented as mean with coefficient of variation (CV). T_{max} and $t_{1/2}$ data are presented as median (range).