DRUG INTERACTIONS WITH DISCONTINUED HEPATITIS C PROTEASE INHIBITORS

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	**Boceprevir (Victrelis®, BOC, SCH 503034) Merck**	**Faldaprevir (FDV, BI201335)**	**Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen**
	Approved in Japan 7/7/2014 **FDA submission for asunaprevir withdrawn by Bristol-Myers Squibb on October 7, 2014:* *Given the rapidly evolving hepatitis C (HCV) treatment landscape in the U.S., Bristol-Myers Squibb has decided that it will not pursue U.S. Food and Drug Administration (FDA) approval of the dual regimen of daclatasvir and asunaprevir for the treatment of HCV genotype 1b patients in the United States and has therefore withdrawn its new drug application (NDA) for asunaprevir, an NS3/4A protease inhibitor.* *Bristol-Myers Squibb's HCV strategy has always been to focus on the unique unmet medical need of each local market. For example, in Japan we were pleased to receive regulatory approval for the dual regimen of daclatasvir and asunaprevir in July,*	***January 2015:*** *Merck has decided to voluntarily discontinue the manufacture and distribution of VICTRELIS in the United States by December 2015. This is a business decision by Merck, and is not based on any safety or efficacy findings.*	**FDA submission for faldaprevir withdrawn by Boehringer Ingelheim on June 18, 2014:* *Boehringer Ingelheim has re-evaluated its strategy in hepatitis C (HCV), and as a result the company has decided not to move forward in this therapeutic area. The HCV treatment environment has significantly and rapidly evolved since the submission of the faldaprevir marketing applications to regulatory bodies around the world. There are now several new treatment options available for patients and additional all-oral options are expected to be approved in 2014. This decision was taken as there is no longer an unmet medical need for the faldaprevir interferon-based regimen that was the subject of the application.* *Boehringer Ingelheim will withdraw all pending marketing applications for faldaprevir worldwide and is discontinuing further development.* *Boehringer Ingelheim*	***August 2014:*** *Vertex Pharmaceuticals announced that it will be discontinuing the sale and distribution of Incivek (telaprevir) tablets in the United States by October 16, 2014.*

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
	bringing Japanese patients with HCV the first all-oral, interferon- and ribavirin-free treatment regimen. The dual regimen was developed to meet the distinct need of the Japanese patient population, and we believe this treatment has the potential to play a major role in curing HCV patients in Japan, as well as in other markets where the HCV patient population is similar to Japan.		*is committed to developing new treatments that provide high therapeutic value in areas where medical need exists. The company is focusing its efforts on numerous promising development projects in immunology, cardiovascular, respiratory, metabolic diseases, diseases of the central nervous system and oncology.*	
Pharmacology	NS3 protease inhibitor	NS3/4A protease inhibitor	NS3/4A protease inhibitor	NS3/4A protease inhibitor
Adult Dose	200 mg BID with food	800 mg po q8h with food (supplied as 200 mg capsules)	*Investigational:* 120 mg QD and 240 mg QD	1125 mg po BID with food (supplied as 375 mg tablets)
Impact of Food		Boceprevir AUC ↑ 60% when administered with a meal vs on an empty stomach. The bioavailability of boceprevir was similar regardless of meal type (e.g., high-fat vs. low-fat) or whether taken 5 minutes prior to eating, during a meal, or immediately following completion of the meal. Therefore, boceprevir may be taken without regard to either meal type or timing.[1]		Compared to a regular breakfast, telaprevir AUC ↓ by 73%, 39% and 26% after administration under fasting conditions, low-calorie/low fat breakfast, and low-calorie/high protein breakfast, respectively. Telaprevir AUC ↑ 20% with a high-fat breakfast.[2] Telaprevir should be taken with food (not low-fat).[3]
Kinetic Characteris	Substrate of CYP3A4 and P-gp. Weak	Boceprevir undergoes biotransformation by	Substrate of CYP3A4. Moderate CYP3A4	Substrate and strong inhibitor of CYP3A4 and

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
tics	inducer of CYP3A4 and P-gp, moderate inhibitor of 2D6.[4] Substrate and weak inhibitor of OATP1B/2B1.[5]	CYP3A4, CYP3A5 and aldoketoreductases.[6] Boceprevir appears to be a strong, reversible inhibitor of CYP3A4 and p-glycoprotein.[7] In a healthy volunteer study, boceprevir does not appear to exert significant P-gp inhibition at clinically relevant concentrations.[8] Boceprevir may induce CYP2C9/2C19 in vivo.[9]	inhibitor at 240 mg dose, weak inhibitor at 120 mg dose.[10] Weak inducer of 2C9 and weak inhibitor of 3A4.[11] CYP1A2, 2B6 and 2D6 activities were not significantly affected by faldaprevir in a healthy volunteer study.[10] Faldeprevir inhibits UGT1A1.	p-glycoprotein.[3] Telaprevir inhibits renal drug transporters OCT2, MATE1, OATP1B1 and OATP1B3.[12]
Effect of hepatic impairment	The pharmacokinetics of multiple dose asunaprenavir 200 mg BID were studied in non-HCV infected subjects with varying degrees of hepatic impairment. In subjects with mild hepatic impairment (Child-Pugh A), ASV Cmax ↓ 42%, AUC ↓ 21% and Cmin ↑ 59% compared to controls. These changes are not considered clinically relevant. Asunaprevir exposures increased substantially in subjects with moderate or severe hepatic impairment (AUC ↑ 9.83-fold in Child-Pugh B and ↑ 32.1-fold in Child-Pugh C) compared to controls; avoid use in moderate-severe hepatic impairment			HCV-negative volunteers with no, mild or moderate hepatic impairment received telaprevir 750 mg as a single dose, then 750 mg q8h for 5 days. All subjects with hepatic impairment were cirrhotics. Mild hepatic impairment did not have a clinically significant effect on telaprevir AUC and Cmax, while moderate hepatic impairment resulted in 49% ↓ Cmax and 46% ↓ AUC of telaprevir compared to controls. A positive correlation between albumin levels and telaprevir exposure was observed.[14] Telaprevir is not is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh B or C, score ≥ 7) or decompensated liver disease. No dose adjustment of telaprevir is necessary for patients with mild hepatic

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
	until further guidance is available.[13]			impairment (Child-Pugh A, score 5-6).[3]
Effect of renal impairment	The kinetics of multiple dose ASV 100 mg BID was assessed in healthy subjects with normal renal function versus subjects with ESRD (est. GFR <15 mL/min/1.73m2). Asunaprevir AUC ↓ 10% and Cmax ↑ 29% in ESRD vs healthy controls. No dose adjustment is needed for ASV in subjects with any level of renal impairment.[15]	In a population pharmacokinetic analysis, no significant covariate effects on boceprevir pharmacokinetic parameters were identified for age, body weight, BMI, Black race, Asian race, renal function and hepatic function. A modest effect of gender (23% ↑ AUC and 22% ↑ Cmax in females) and HCV status (15-20% ↓ Cmax) was observed, but not anticipated to be clinically meaningful.[16]	The kinetics of single-dose faldaprevir 480 mg was assessed in subjects with normal renal function or mild, moderate or severe renal impairment. A moderate increase in FDV exposures was observed in subjects with moderate-severe renal impairment was observed, but protein binding assessment indicated no difference in free FDV between the groups. There was no difference in tolerability of FDV between the groups. Dose adjustment in renal impairment is not warranted.[17]	No dose adjustment is recommended for telaprevir in HCV-infected patients with mild, moderate or severe renal impairment.[3]
DAA Interactions:				
BMS-791325 (non-nucleoside of NS5B polymerase)	In HCV GT-1 subjects, BMS-791325 dosed at 75mg and 150mg BID was administered with daclatasvir (DVC) 60mg daily and asunaprevir 200mg BID for 12 or 24 weeks. After 14 days, DCV and BMS-791325 exposure were comparable to historical data. ASV exposure was reduced by 30% but variability was high.[18]			
Daclatasvir	No clinically meaningful interaction observed in healthy volunteers.[19]	Potential for increased daclatasvir exposures due to CYP3A4 inhibition by boceprevir. Reduce		With coadministration of telaprevir 750 mg q8h and daclatasvir 20 mg daily, daclatasvir AUC increased 115%, Cmax

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		daclatasvir dose to 30 mg once daily when coadministered with boceprevir or other strong inhibitors of CYP3A4.[20]		increased 22%, and telaprevir exposures were unchanged. Reduce daclatasvir dose to 30 mg once daily when coadministered with telaprevir or other strong inhibitors of CYP3A4.[20]
Deleobuvir (BI 207127, non-nucleoside NS5B inhibitor; ***no longer in development***)			HCV-genotype 1 subjects were randomized to an 8 day lead-in of either faldeprevir 120 mg daily or deleobuvir 600 mg daily each with pegylated interferon alpha-2a/ribavirin, followed by 24 weeks of 120 mg daily faldaprevir plus 600 mg TID deleobuvir plus ribavirin. After 8 weeks of combined treatment, FDV concentrations were similar to those observed prior to deleobuvir dosing, while deleobuvir AUC ↑ 199%, Cmax ↑ 176% and Cmin ↑ 245% relative to pre-dual DAA exposure.[11]	
Antiretroviral Interactions:				
Atazanavir/ ritonavir		In healthy volunteers, coadministration of boceprevir and atazanavir/ritonavir resulted in 49% ↓ Ctrough, 35% ↓ AUC and 25% ↓ Cmax of atazanavir and ↓ 34% ritonavir AUC; boceprevir exposures were not altered.[21] In a pharmacokinetic substudy of ACTG	In a PK substudy of the STARTVerso4 trial, 12 HIV-HCV coinfected subjects on ATV/r received faldaprevir 120 mg QD plus peg-IFN/ribavirin. Atazanavir PK parameters were not significantly changed in the presence of faldaprevir. Compared to historical data, steady-state	In an open-label, randomized, cross-over study, 20 HIV/HCV-negative volunteers received 2 treatments: telaprevir 750 mg every 8 hours for 10 days followed by a washout and ATV/r 300/100 mg once daily for 20 days with co-administration of telaprevir 750 mg every 8 hours from day 11 onwards, or *vice versa*.

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		A5294, HIV/HCV coinfected subjects on boosted atazanavir (n=11) experienced 30% ↓ AUC and 43% ↓ Cmin of atazanavir during boceprevir therapy compared to baseline. Boceprevir pharmacokinetics in the presence of atazanavir/ritonavir were not significantly different from historical data. These effects are similar to those observed in healthy volunteers.[22] Coadministration of boceprevir and ritonavir-boosted protease inhibitors is not recommended.[1] The European Medicine Agency stated that coadministration of boceprevir with ritonavir-boosted atazanavir may be considered on a case-by-case basis if deemed necessary in patients with suppressed HIV viral loads and with an HIV strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring is warranted in such cases.[23] In an open-label, phase II trial of treatment-experienced HIV/HCV genotype 1	faldaprevir AUC, Cmax and C24h were increased 76%, 67% and 119%, respectively. Faldaprevir 120 mg QD may be coadministered with atazanavir/ritonavir.[25]	All compounds were taken with food. With coadministration, telaprevir AUC ↓ 20% and Cmin ↓ 15%, while atazanavir AUC ↑ 17% and Cmin ↑ 85%.[26] In a pharmacokinetic substudy of ANRSHC26, the pharmacokinetics of atazanavir/ritonavir with pegylated interferon/ribavirin or with pegylated interferon/ribavirin/telaprevir were assessed in 16 HIV-HCV coinfected subjects. Twelve subjects completed all samples for PK analysis. In the presence of telaprevir, atazanavir Cmin increased 79% despite a lower (35% decrease AUC) exposure to ritonavir. This was associated with a mild increase in bilirubin concentrations.[27] In HIV/HCV co-infected subjects participating in a phase 2 randomized study of telaprevir vs. placebo plus pegylated-interferon plus ribavirin, the kinetics of telaprevir were compared in patients on stable ATV/r therapy to patients not receiving concomitant antiretroviral therapy. In patients receiving concomitant ATV/r, telaprevir Cavg was 9% ↑ compared to patients

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		patients virologically suppressed on atazanavir/ritonavir-based cART (n=7), pharmacokinetic parameters were assessed at baseline and after 4 weeks of BOC 800 mg TID with ribavirin/pegylated interferon. Compared to baseline, mean atazanavir AUC ↓ 51%, Ctau ↓ 34% and Cmax ↓ 41% in the presence of BOC/ribavirin/peg-IFN; mean atazanavir Ctau was 507.7 ug/L compared to 763.8 ug/L at baseline.[24]		not receiving concomitant antiretroviral therapy. Median atazanavir concentrations were 16% higher during telaprevir treatment vs. before HCV treatment. Dose adjustment is not required when atazanavir/ritonavir is administered with telaprevir.[28] In an open-label sequential study in HIV/HCV coinfected subjects on an atazanavir/ritonavir-based regimen plus triple therapy with telaprevir 1125 mg BID, pharmacokinetic profiles were acquired before and after switching from boosted to **unboosted atazanavir 200 mg q12h**. After ritonavir was withdrawn, telaprevir AUC, Cmax and Cmin increased by 19%, 12% and 18%, respectively, while atazanavir AUC, Cmax and Cmin increased by 39%, 19% and 48%, respectively.[29] In healthy subjects, coadministration of elvitegravir 85 mg/atazanavir 300 mg/ritonavir 100 mg daily plus telaprevir 750 mg TID for 10 days did not result in clinically relevant changes in the pharmacokinetics of elvitegravir, atazanavir or telaprevir

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
				pharmacokinetics. Combination may be coadministered without dose adjustment.[30]
Darunavir/ ritonavir		In healthy volunteers, coadministration of boceprevir and darunavir/ritonavir resulted in 59% ↓ Ctrough, 44% ↓ AUC and ↓ 36% Cmax of darunavir and 27% ↓ ritonavir AUC, while boceprevir exposure was ↓ by 32%.[21] In a pharmacokinetic substudy of ACTG A5294, HIV/HCV coinfected subjects on darunavir/ritonavir BID (n=5) experienced 42% ↓ AUC, 32% ↓ Cmax and 64% ↓ Cmin of darunavir during boceprevir therapy compared to baseline. Boceprevir Cmin was 93% higher with no differences in AUC or Cmax in the presence of darunavir/ritonavir compared to historical data. These effects are similar to those observed in healthy volunteers.[22] Coadministration of boceprevir and ritonavir-boosted protease inhibitors is not recommended.[1]	In an open-label study, 14 healthy subjects (86% male) received darunavir 800/ritonavir 100 mg QD on days 1–16, a loading dose of faldaprevir 480 mg QD on day 9, and faldaprevir 240 mg QD on days 10–16. Faldaprevir Cmax ↑ 64%, AUC ↑ 129% and Cmin ↑ 283% in the presence of boosted darunavir, while darunavir Cmax ↑ 28%, AUC ↑ 15% and Cmin ↓12% with concomitant faldaprevir. Impact on darunavir kinetics not considered clinically relevant.[31] In an interim analysis from STARTVerso4, darunavir trough concentrations were decreased 48% in the presence of concomitant faldaprevir 120 mg daily.[32]	In an open-label, randomized, cross-over study, 20 HIV/HCV-negative volunteers received 2 treatments: telaprevir 750 mg every 8 hours for 10 days, followed by a washout and DRV/r 600/100 mg twice daily for 20 days with co-administration of telaprevir 750 mg every 8 hours from day 11 onwards, or *vice versa*. All compounds were taken with food. With coadministration, telaprevir AUC ↓ 35% and Cmin ↓ 32%, while darunavir AUC ↓ 40% and Cmin ↓ 42%.[26] Darunavir/ritonavir and telaprevir should not be co-administered.[3] In 14 HIV/HCV coinfected patients on stable cART including darunavir 800/ritonavir 100 mg daily, initiation of telaprevir 750 mg TID plus pegylated interferon and ribavirin led to a reduction in total and unbound darunavir plasma concentrations (total darunavir Cmin ↓ 39%, AUC ↓ 47%, while unbound darunavir Cmin ↓ 33% and AUC ↓ 46%) compared to darunavir concentrations prior to starting telaprevir.

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
				Mean total concentrations of telaprevir were reduced compared with historical data, but appeared similar to the lowest quartile observed in prior telaprevir studies.[33] Similarly, in two HIV/HCV coinfected individuals receiving darunavir 800/100 mg QD, complete steady-state PK study was performed before and 4 weeks after starting telaprevir 750 mg TID. In the presence of telaprevir, darunavir total AUC ↓ 68-75% and unbound AUC ↓ 53-66%, total Cmax ↓ 70% and unbound Cmax ↓ 46-54% compared to baseline. In one patient, darunavir total Ctrough ↓ 97% and unbound Ctrough ↓ 93%, while in the second patient, total Ctrough ↓ 58% but unbound Ctrough ↑ 207%. Both patients completed 12 weeks of triple therapy and their HIV remained virologically suppressed.[34]
Dolutegravir		In healthy subjects, coadministration of dolutegravir 50 mg QD with BOC 800 mg TID for 10 days had no effect on plasma dolutegravir AUC or Cmax, while Ctau ↑ 8% compared to dolutegravir 50 mg QD administered alone.		In healthy subjects, coadministration of dolutegravir 50 mg QD with TVR 750 mg TID for 10 days resulted in 25% ↑ AUC, 19% ↑ Cmax and 37% ↑ Ctau of dolutegravir compared to dolutegravir 50 mg QD administered alone.

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		Dolutegravir may be administered with boceprevir without dose adjustment.[35, 36]		Telaprevir exposures in the presence of dolutegravir were similar to historical controls. Dolutegravir may be administered with telaprevir without dose adjustment.[35, 36]
Efavirenz		In healthy subjects, there was a slight reduction in BOC $AUC_{(0\text{-}8h)}$ and C_{max} (19% and 8%, respectively), and a 44% decrease in BOC C_{min} when co-administered with efavirenz. BOC slightly increased EFV $AUC_{(0\text{-}24h)}$ and C_{max} (20% and 11%, respectively).[7] In a pharmacokinetic substudy of ACTG A5294, HIV/HCV coinfected subjects on efavirenz (n=19) did not experience significant alterations in efavirenz pharmacokinetics during boceprevir therapy compared to baseline. Boceprevir Cmin ↓ 21%, AUC ↓ 11% and Cmax ↓ 27% in the presence of efavirenz compared to historical data. These effects are similar to those observed in healthy volunteers.[22] **Avoid combination**.[1]	In an open-label study, 15 healthy subjects (60% male) received faldaprevir 240 mg BID on days 2–18, efavirenz 600 mg QD on days 10–18, and oral midazolam 7.5 mg QD to study effects on CYP3A4 on days 1, 9, and 18. Faldaprevir Cmax ↓ 28%, AUC ↓ 35% and Cmin ↓ 46% in the presence of efavirenz. Midazolam AUC was ↑ 125% with faldaprevir and ↓ 61% with faldaprevir plus efavirenz compared to midazolam administered alone.[31] In an interim analysis from STARTVerso4, efavirenz concentrations were not significantly decreased in the presence of concomitant faldaprevir 240 mg daily.[32]	In healthy volunteers, multiple-dose administration of efavirenz 600 mg daily and telaprevir 750 mg q8h resulted in 9% ↓ Cmax, 47% ↓ Cmin and 26% ↓ AUC of telaprevir.[37] In an open-label study, 20 HIV/HCV-negative volunteers started telaprevir 750 mg every 8 hours for 7 days followed by EFV/tenofovir disoproxil fumarate (TDF) 600/300 mg once daily for 7 days after a washout. Subsequently, volunteers received telaprevir 1125 mg every 8 hours and EFV/TDF 600/300 mg once daily for 7 days or telaprevir 1500 mg every 12 hours and EFV/TDF 600/300 mg once daily for 7 days in a randomized order without a washout. Telaprevir was taken with food and EFV/TDF was taken on an empty stomach in the morning. With TVR 1125 mg q8h plus efavirenz/TDF, telaprevir AUC ↓ 18%, Cmin ↓ 25%, EFV AUC ↓ 18%, Cmin ↓ 10%,

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
				and tenofovir AUC ↑ 10% and Cmin ↑ 17%. With TVR 1500 mg q12h plus EFV/TDF, telaprevir AUC ↓ 20%, Cmin ↓ 48%, EFV AUC ↓ 15%, Cmin ↓ 11%, and tenofovir AUC ↑ 10% and Cmin ↑ 6%.[26] In HIV/HCV co-infected subjects participating in a phase 2 randomized study of telaprevir vs. placebo plus pegylated-interferon plus ribavirin, the kinetics of telaprevir 1125 mg q8h were compared in patients on stable efavirenz therapy to patients on telaprevir 750 mg q8h not receiving concomitant antiretroviral therapy. In patients receiving efavirenz, telaprevir Cavg was 4% ↓ compared to patients not receiving concomitant antiretroviral therapy. Median efavirenz concentrations were 6% lower during telaprevir treatment vs. before HCV treatment. A higher dose of telaprevir (1125 mg every 8 hours) given with efavirenz provides similar telaprevir exposures as seen in the absence of efavirenz.[28]
Elvitegravir/ cobicistat		Potential for concentrations of DAA and/or elvitegravir/cobicistat to be affected; avoid coadministration until		In healthy volunteers, coadministration of telaprevir 750 mg TID with elvitegravir/ cobicistat/tenofovir/emtricitabine (Stribild®) for

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		more data are available.		10 days did not result in clinically relevant changes in pharmacokinetic exposures of Stribild® or telaprevir. The combination may be coadministered without dosage adjustment.[38]
Etravirine		In healthy volunteers, coadministration of boceprevir 800 mg q8h with etravirine 200 mg BID for 11-14 days resulted in ↓ 23% AUC, ↓ 24% Cmax and ↓29% Cmin of etravirine and ↑10% AUC and Cmax and ↓ 12% Cmin of boceprevir compared to either drug administered alone. Impact on boceprevir concentrations not considered clinically relevant; impact on etravirine concentrations could be clinically significant.[39] Mechanism of interaction postulated to be induction of CYP2C9/19 by etravirine.[9] The combination of etravirine and boceprevir can be used without dose adjustments. However, co-administration of etravirine and boceprevir is not recommended in the presence of other drugs which may		In healthy volunteers, coadministration of telaprevir 750 mg TID with etravirine 200 mg BID for 11 days resulted in ↓ 6% AUC, ↓ 7% Cmax and ↓3% Cmin of etravirine and ↓ 16% AUC, ↓ 10% Cmax and ↓ 25% Cmin of telaprevir compared to either drug administered alone. These changes are not considered clinically relevant, combination may be given without dose adjustment.[40]

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		further decrease etravirine exposure. This includes, but is not limited to, darunavir/ritonavir, lopinavir/ritonavir, saquinavir/ritonavir, te nofovir disoproxil fumarate, or rifabutin.[Intelence® revised Product Label, August 2014, Janssen, USA]		
Fosamprenavir/ ritonavir		Coadministration of boceprevir and ritonavir-boosted protease inhibitors is not recommended.[1]		In an open-label, randomized, cross-over study, 20 HIV/HCV-negative volunteers received 2 treatments: telaprevir 750 mg every 8 hours for 10 days, followed by a washout and fosamprenavir/r 700/100 mg twice daily for 20 days with co-administration of telaprevir 750 mg every 8 hours from day 11 onwards, or *vice versa*. All compounds were taken with food. With coadministration, telaprevir AUC ↓ 32% and Cmin ↓ 30%, while amprenavir AUC ↓ 47% and Cmin ↓ 56%.[26] Fosamprenavir/ritonavir and telaprevir should not be co-administered.[3]
Lopinavir/ritonavir		In healthy volunteers, coadministration of boceprevir and lopinavir/ritonavir resulted in 43% ↓ Ctrough, 34% ↓ AUC and ↓ 30% Cmax of lopinavir and 22% ↓ ritonavir AUC, while boceprevir exposure		In an open-label, randomized, cross-over study, 20 HIV/HCV-negative volunteers received 2 treatments: telaprevir 750 mg every 8 hours for 10 days, followed by a washout and lopinavir/r 400/100 mg twice daily for 20

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		was ↓ by 45%.[21] Coadministration of boceprevir and ritonavir-boosted protease inhibitors is not recommended.[1]		days with co-administration of telaprevir 750 mg every 8 hours from day 11 onwards, or *vice versa*. All compounds were taken with food. With coadministration, telaprevir AUC ↓ 54% and Cmin ↓ 52%, while lopinavir AUC ↑ 6% and Cmin ↑ 14%.[26] Lopinavir/ritonavir and telaprevir should not be co-administered.[3]
Maraviroc		In an open-label, fixed sequence study, 13 healthy volunteers received maraviroc 150 mg BID for 5 days, followed by BOC 800 mg TID plus maraviroc 150 mg BID for 10 days, then after a 10-day washout period, TVR 750 mg TID plus maraviroc 150 mg BID for 10 days. In the presence of BOC, maraviroc GMR for AUC was 3.02, Cmax 3.33, and C12 2.78 versus maraviroc administered alone. Boceprevir pharmacokinetics were similar to historical controls. The mean maraviroc Cavg was 151 ng/mL in combination with boceprevir.[41] In an open-label, crossover, single sequence study, healthy volunteers (n=5) received		In an open-label, fixed sequence study, 13 healthy volunteers received maraviroc 150 mg BID for 5 days, followed by BOC 800 mg TID plus maraviroc 150 mg BID for 10 days, then after a 10-day washout period, TVR 750 mg TID plus maraviroc 150 mg BID for 10 days. In the presence of TVR, maraviroc GMR for AUC was 9.49, Cmax 7.81, and C12 10.17 versus maraviroc administered alone. Telaprevir pharmacokinetics were similar to historical controls. The mean maraviroc Cavg was 465 ng/mL in combination with telaprevir. Maraviroc should be dosed at 150 mg BID when coadministered with telaprevir.[41]

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		maraviroc 150 mg BID for 5 days followed by BOC 800 mg TID plus maraviroc 150 mg BID for 14 days. In the presence of BOC, maraviroc GMR for AUC was 2.28, Cmax 1.25, and Ctau 3.62 versus maraviroc administered alone. The mean maraviroc Ctau was 30 ng/mL (CV 69%) with BOC, versus 7 ng/mL (CV 52%) alone.[42] Maraviroc should be dosed at 150 mg BID when coadministered with boceprevir.[41, 42]		
Raltegravir	In a pharmacokinetic substudy of ANRS HC30 involving HIV/HCV coinfected subjects who were previous null responders on stable raltegravir-based therapy, subjects received 4 weeks of pegylated interferon/ ribavirin, followed by the addition of asunaprevir 100 mg BID and daclatasvir 60 mg daily for 24 weeks. Pharmacokinetic measurements were conducted at baseline and 4 weeks after initiation of asunaprevir and daclatasvir. Exposures of asunaprevir and daclatasvir were similar to those reported in mono-	In an open-label, randomized, cross-over study, 24 healthy volunteers, received boceprevir 800 mg TID for 10 days plus single dose raltegravir 400 mg on day 10 followed by a wash-out period and single-dose raltegravir 400 mg on day 38, or the same medications in reverse order. Raltegravir exposures were not altered in the presence of boceprevir. The combination may be used without dosage adjustment.[44] In a pharmacokinetic substudy of ACTG A5294, HIV/HCV coinfected subjects on raltegravir BID (n=17) experienced 56% ↑ AUC, 87% ↑ Cmax of raltegravir during	In an open-label, 2 period study in healthy subjects, coadministration of raltegravir 400 mg BID plus faldaprevir 240 mg QD resulted in ~2.7-fold increase in raltegravir exposures.[46] In an interim analysis from STARTVerso4, raltegravir trough concentrations were decreased 5% and 29% in the presence of concomitant faldaprevir 120 mg and 240 mg daily, respectively. These changes are not considered clinically relevant.[32] No dose adjustment is required with concomitant administration of	In an open-label cross-over study in 20 HIV/HCV-negative healthy volunteers, co-administration of raltegravir 400 mg BID and telaprevir 750 mg q8h for 6 days with food did not affect telaprevir pharmacokinetics, while raltegravir exposures were increased (Cmin ↑ 78%, Cmax ↑ 26% and AUC ↑ 31%) possibly due to inhibition of intestinal P-gp by telaprevir. Exposure to raltegravir-glucuronide was similarly increased. This effect was not considered to be clinically relevant.[47] No dose adjustment is needed for telaprevir when given with raltegravir. The safe use of

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
	infected subjects, and raltegravir pharmacokinetics remained in a similar range after initiation of the DAAs.[43]	boceprevir therapy compared to baseline. Boceprevir AUC was 18%% higher with no differences in Cmin or Cmax in the presence of raltegravir compared to historical data.[22] The safe use of raltegravir-based therapy in HIV-patients with HCV-cirrhosis receiving triple therapy with boceprevir (n=2) or telaprevir (n=9) has been reported. Median baseline CD4 was 556 cells/mm3, all subjects had undetectable viral load, and all subjects had compensated cirrhosis (Child-Pugh score ≤6 in 82%). During 12 weeks of triple therapy, HIV viral suppression was maintained in all patients except one due to nonadherence. 73% patients achieved complete early HCV virologic response (negative HCV-RNA at week 12 of therapy) with no breakthrough or recurrence during follow-up.[45] In an open-label, phase II trial of treatment-experienced HIV/HCV genotype 1 patients virologically suppressed on raltegravir-based cART (n=5), pharmacokinetic parameters were	faldaprevir and raltegravir.	raltegravir-based therapy in HIV-patients with HCV-cirrhosis receiving triple therapy with boceprevir (n=2) or telaprevir (n=9) has been reported. Median baseline CD4 was 556 cells/mm3, all subjects had undetectable viral load, and all subjects had compensated cirrhosis (Child-Pugh score ≤6 in 82%). During 12 weeks of triple therapy, HIV viral suppression was maintained in all patients except one due to nonadherence. 73% patients achieved complete early HCV virologic response (negative HCV-RNA at week 12 of therapy) with no breakthrough or recurrence during follow-up.[45]

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		assessed at baseline and after 4 weeks of BOC 800 mg TID with ribavirin/pegylated interferon. Compared to baseline, mean raltegravir AUC ↑ 57%, Ctau ↓ 55% and Cmax ↑ 156% in the presence of BOC/ribavirin/peg-IFN.[24]		
Rilpivirine		In healthy volunteers (n=20), coadministration of boceprevir 800 mg TID and rilpivirine 25 mg QD for 11 days resulted in 39% ↑ AUC, 15% ↑ Cmax and 51% ↑ C24h of rilpivirine. The combination was well-tolerated, and these changes were not considered clinically significant. Boceprevir kinetics were not affected by coadministration of rilpivirine. Boceprevir and rilpivirine may be coadministered without dose adjustment.[48]		In healthy volunteers, coadministration of telaprevir 750 mg TID with rilpivirine 25 mg daily for 11 days resulted in ↑ 78% AUC, ↑ 49% Cmax and ↑ 93% Cmin of rilpivirine and ↓ 8% AUC, ↓ 5% Cmax and ↓ 13% Cmin of telaprevir compared to either drug administered alone. These changes are not considered clinically relevant, combination may be given without dose adjustment.[40] May wish to avoid using combination in patients at increased risk for Torsade de Pointes, or who are on other drugs that may ↑ rilpivirine levels or that are known to cause QTc prolongation.
Ritonavir		In human liver microsomes, the metabolism of telaprevir and boceprevir was substantially inhibited in the presence of low concentrations of ritonavir. With co-		In human liver microsomes, the metabolism of telaprevir and boceprevir was substantially inhibited in the presence of low concentrations of ritonavir. With co-dosing of ritonavir in

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		dosing of ritonavir in rats, the plasma exposure of both HCV agents was increased by more than 15-fold, and plasma concentrations 8 hours after dosing were increased by > 50-fold.[49] In healthy subjects, ritonavir had minimal effects on steady-state BOC exposure. RTV 100 mg daily plus BOC three times daily resulted in BOC AUC ↓ 19% and Cmax ↓ 27%, while ritonavir 100mg BID plus BOC twice daily resulted in decreased BOC AUC by 18% and Cmax ↓ 34%.[7]		rats, the plasma exposure of both HCV agents was increased by more than 15-fold, and plasma concentrations 8 hours after dosing were increased by > 50-fold. A human pharmacokinetic model of telaprevir co-administered with low-dose ritonavir suggested that improved efficacy and/or dosing convenience may be feasible by pharmacokinetic enhancement with ritonavir.[49] HIV-negative subjects received telaprevir 750 mg q8h alone, or 250 mg or 750 mg BID with ritonavir 100 mg BID. Doses were given with food for 14 days. Ritonavir did not exert a significant boosting effect on telaprevir exposures: when compared with TVR 750 mg q8h given alone (Group C), TVR PK parameters on Day 14 were 59% to 75% lower when TVR 250 mg q12h was co-administered with RTV 100 mg q12h (Group A) and 15% to 32% lower when TVR 750 mg q12h was co-administered with RTV 100 mg q12h (Group B). Of note, RTV exposures were higher when co-administered with TVR 750 mg q12h (Group B), compared with 250

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
				q12h (Group A), suggesting that CYP3A inhibition by TVR was dose-dependent.[50]
Tenofovir		In healthy subjects, there were no clinically relevant changes in BOC exposure when co-administered with tenofovir. BOC also had no notable effect on tenofovir AUC or renal clearance, but increased tenofovir C_{max} by 32%. No BOC dosage adjustment is needed with co-administration tenofovir.[7]	In an open-label study, 16 healthy subjects (81% male) received tenofovir 300 mg QD on days 1–10 and faldaprevir 240 mg BID on days 8–22. Faldaprevir Cmax ↓ 18%, AUC ↓ 22% and Cmin ↓ 25% in the presence of tenofovir, while tenofovir Cmax ↓ 5%, AUC ↑ 22% and Cmin ↑ 47% with concomitant faldaprevir. Impact on tenofovir kinetics not considered clinically relevant.[31] In an interim analysis from STARTVerso4, tenofovir trough concentrations were not significantly altered in the presence of concomitant faldaprevir 120 mg daily or 240 mg daily with or without efavirenz.[32]	In a randomized, open-label study, healthy volunteers received tenofovir 300 mg daily, telaprevir 750 mg q8h, or both drugs, each for 7 days. In the presence of telaprevir, tenofovir AUC_{24h} was increased by 30% while telaprevir kinetics were not affected.[51] In an open-label study, 20 HIV/HCV-negative volunteers started telaprevir 750 mg every 8 hours for 7 days followed by EFV/tenofovir disoproxil fumarate (TDF) 600/300 mg once daily for 7 days after a washout. Subsequently, volunteers received telaprevir 1125 mg every 8 hours and EFV/TDF 600/300 mg once daily for 7 days or telaprevir 1500 mg every 12 hours and EFV/TDF 600/300 mg once daily for 7 days in a randomized order without a washout. Telaprevir was taken with food and EFV/TDF was taken on an empty stomach in the morning. With TVR 1125 mg q8h plus efavirenz/TDF/FTC, telaprevir AUC ↓ 18%, Cmin ↓ 25%, EFV AUC ↓ 18%, Cmin ↓ 10%, and tenofovir AUC ↑

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
				10% and Cmin ↑ 17%. With TVR 1500 mg q8h plus EFV/TDF/FTC, telaprevir AUC ↓ 20%, Cmin ↓ 48%, EFV AUC ↓ 15%, Cmin ↓ 11%, and tenofovir AUC ↑ 10% and Cmin ↑ 6%.[26]
Other Drugs:				
Amlodipine		Combination not studied. Potential for ↑ amlodipine concentrations in the presence of boceprevir. Use combination with caution and monitor for dose-related amlodipine toxicity.		In healthy subjects, the kinetics of single dose amlodipine 5 mg/atorvastatin 20 mg (coformulated) were assessed alone and with steady-state telaprevir 750 mg q8h. In the presence of telaprevir, amlodipine Cmax ↑ 27% and AUC ↑ 179%. Monitor for dose-related amlodipine toxicity when coadministering with telaprevir.[52]
Buprenorphine/naloxone	The effect of steady-state asunaprevir 100 mg BID on the kinetics of methadone (40-120 mg daily) or buprenorphine/naloxone (8/2-24/6 mg daily) was assessed in subjects on stable opioid therapy. Asunaprevir had no clinically meaningful effect on the pharmacokinetics of methadone or buprenorphine/naloxone and was generally well-tolerated. No dose adjustment is required with coadministration.[53]	In HCV-negative volunteers on stable, maintenance doses (8/2 mg to 24/6 mg QD) of buprenorphine/naloxone, coadministration of boceprevir 800 mg q8h for 6 days did not have a clinically significant impact on the pharmacokinetics of buprenorphine (AUC ↑ 20%, Cmax ↑ 18%) or naloxone (AUC ↑ 30%, Cmax ↑ 9%). Boceprevir exposures in the presence of buprenorphine/naloxone were similar to historical controls. Dose adjustment is likely not necessary when boceprevir is co-	In 19 subjects on stable buprenorphine/naloxone maintenance therapy, administration of 480 mg faldaprevir (loading dose) followed by 240 mg QD faldaprevir for 7 days resulted in <10% ↑ in buprenorphine and naloxone exposures. There was no evidence of withdrawal as evaluated by the validated OOWS or SOWS scores. No dose adjustment is required for buprenorphine/ naloxone when coadministered with faldaprevir.[55]	In HCV-negative volunteers on stable, maintenance doses of buprenorphine/naloxone, coadministration of telaprevir 750 mg q8h for 7 days did not have a clinically significant impact on the pharmacokinetics or pharmacodynamic effects of buprenorphine. Telaprevir exposure was consistent with historical control when co-administered with buprenorphine/naloxone. Dose adjustment is not necessary when telaprevir is co-administered with buprenorphine/naloxone

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		administered with buprenorphine/naloxone.[54]		.[56]
Clarithromycin		In healthy subjects, clarithromycin had minimal effects on steady-state BOC exposure. Clarithromycin (in the presence of diflunisal) increased BOC AUC by 21% and Cmax by 36%.[7]		
Corticosteroids (oral/inhaled, injectable or topical) e.g., betamethasone, budesonide, dexamethasone, fluticasone, prednisone, triamcinolone		Inhaled/nasal fluticasone and budesonide: Potential for ↑ corticosteroid concentrations resulting in significantly reduced serum cortisol concentrations. Avoid co-administration if possible, particularly for extended durations.[1] Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[57] Systemic dexamethasone: Potential for ↓ boceprevir concentrations via CYP3A4 induction by dexamethasone.		Inhaled/nasal fluticasone and budesonide: Potential for ↑ corticosteroid concentrations resulting in significantly reduced serum cortisol concentrations. Co-administration of fluticasone or budesonide and telaprevir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.[3] Inhaled beclomethasone or ciclesonide, or intranasal beclomethasone or triamcinolone may be safer alternatives, but caution is still warranted. Use lowest possible corticosteroid dose and monitor closely for systemic corticosteroid side effects.[57] Systemic dexamethasone: Potential for ↓ telaprevir

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		Avoid combination if possible, use with caution if necessary.[1] <u>Prednisone:</u> In healthy volunteers, steady-state boceprevir 800 mg TID did not significantly affect the pharmacokinetics of single-dose prednisone 40 mg (prednisone AUC ↑ 22%, prednisolone AUC ↑ 37%). These results suggest that no dosage adjustment is necessary, but patients should be monitored appropriately for potential toxicities associated with prolonged increases in prednisolone exposure.[58]		concentrations via CYP3A4 induction by dexamethasone. Use combination with caution or consider alternate agents.[3]
Digoxin	The pharmacokinetics of single dose digoxin 0.5 mg was assessed alone and in the presence of steady-state asunaprevir 200 mg BID in 16 healthy adult subjects. Digoxin AUC increased 30% and Cmax increased 8% in the presence of concomitant asunaprevir, confirming that asunaprevir is a weak Pgp inhibitor.[4] The combined effect of daclatasvir 60 mg daily plus asunaprevir 100 mg	In an open-label, randomized crossover study, healthy volunteers received single dose digoxin 0.25 mg alone or in combination with multiple-dose boceprevir 800 mg TID. In the presence of boceprevir, digoxin AUC was ↑ 19% and Cmax ↑ 18%, while terminal t½ was unchanged. These results suggest that dosage adjustment of digoxin is not necessary with concomitant boceprevir therapy, and that boceprevir does not appear to		In an open-label study, healthy subjects received single doses of IV midazolam 0.5 mg, and oral midazolam 2 mg with oral digoxin 0.5 mg administered sequentially alone and in combination with multiple-dose telaprevir 750 mg q8h. In the presence of telaprevir, digoxin Cmax ↑ 50% and AUC ↑ 85%, while renal clearance was not changed.[60] Initiate digoxin at the lowest dose, and monitor serum digoxin concentrations to titrate to desired clinical effect.[3]

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
	BID on the pharmacokinetics of single dose digoxin 0.25 mg in healthy subjects was assessed. Digoxin Cmax increased 77% and AUC increased 29% in the presence of daclatasvir plus asunaprevir. This effect is similar to that of daclatasvir alone plus digoxin. Caution is warranted when dosing daclatasvir plus asunaprevir with digoxin and other P-gp substrates with a narrow therapeutic window; a priori dose modification does not appear to be required. Therapeutic drug monitoring, if available, may be considered.[59]	exert significant P-gp inhibition at clinically relevant concentrations.[8] Patients receiving treatment with both boceprevir and digoxin should be monitored appropriately.[1]		
Eltrombopag		In healthy volunteers, the pharmacokinetics of single-dose eltrombopag 200 mg given alone or in the presence of steady-state boceprevir 800mg q8h was assessed. Boceprevir Cmax increased 20%, Ctau decreased 32% while AUC was unchanged when coadministered with eltrombopag; eltrombopag pharmacokinetics were not altered in the presence of boceprevir. Dose adjustment is not required when		In healthy volunteers, the pharmacokinetics of single-dose eltrombopag 200 mg given alone or in the presence of steady-state telaprevir 750 mg q8h was assessed. Neither telaprevir nor eltrombopag pharmacokinetics were altered when the drugs were coadministered. Dose adjustment is not required when eltrombopag is coadministered with telaprevir.[61]

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		eltrombopag is coadministered with boceprevir.[61]		
Escitalopram	Healthy subjects received escitalopram 10 mg daily or sertraline 50 mg daily, alone or in combination with steady-state asunaprevir 100 mg BID. Asunaprevir did not affect the exposures of either escitalopram or sertraline, and escitalopram and sertraline did not affect exposures of asunaprevir to a clinically-relevant degree. These agents may be coadministered without dose adjustments.[62]	In healthy volunteers, the kinetics of single dose escitalopram 10 mg were not altered to a clinically significant manner in the presence of multiple dose boceprevir 800 mg TID. The pharmacokinetics of boceprevir were similar with and without coadministration of escitalopram. No dosage adjustment is expected to be required with coadministration of this combination.[63]		In healthy volunteers, coadministration of escitalopram 10 mg daily with telaprevir 750 mg q8h for 7 days resulted in 35% ↓ escitalopram AUC, while telaprevir exposures were not affected. May need to titrate escitalopram dose according to clinical response.[64]
HmgCoA reductase inhibitors (statins): atorvastatin lovastatin pravastatin rosuvastatin simvastatin	In healthy subjects, administration of single dose rosuvastatin 10 mg alone or with steady-state asunaprevir 200 mg BID led to 95% ↑ Cmax and 41% ↑ AUC of rosuvastatin, likely via inhibition of OATP1B1 by asunaprevir.[5]	In healthy volunteers, the kinetics of single dose **atorvastatin 40 mg** in the presence of steady-state BOC 800 mg TID were significantly increased (atorvastatin AUC ↑ 130% and Cmax ↑ 170%) compared to administration alone. BOC kinetics were not significantly affected by atorvastatin coadministration. A lower maintenance dose of atorvastatin may be warranted with concomitant BOC therapy; additional clinical monitoring for symptoms of statin toxicity is		In healthy subjects, the kinetics of single dose amlodipine 5 mg/atorvastatin 20 mg (coformulated) were assessed alone and with steady-state telaprevir 750 mg q8h. In the presence of telaprevir, atorvastatin Cmax ↑ 10.6-fold and AUC ↑ 7.88-fold.[52] **Atorvastatin, lovastatin and simvastatin are contraindicated with telaprevir**.[66]

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		recommended if atorvastatin doses of greater than 40 mg daily are used.[65] In healthy volunteers, the kinetics of single dose **pravastatin 40 mg** in the presence of steady-state BOC 800 mg TID were increased (pravastatin AUC ↑ 60% and Cmax ↑ 50%) compared to administration alone. BOC kinetics were not significantly affected by pravastatin coadministration. This slight increase may reflect potential inhibition of OATP by BOC, since pravastatin is not metabolized to a significant extent by CYP450 and is a substrate of OATP1B1 and OATP2B1, but not of P-gp. It is anticipated that pravastatin treatment can be initiated at the recommended dose when co-administered with BOC, with close clinical monitoring.[65] **Lovastatin and simvastatin are contraindicated with boceprevir**.[66]		
Ketoconazole	In healthy subjects who received asunaprevir 200 mg BID alone or with multi-dose ketoconazole 200 mg BID, asunaprevir exposures were	In healthy subjects, ketoconazole (KCZ) increased BOC AUC ↑131%, Cmax ↑ 41%.[7] When coadministration is required, doses of ketoconazole and		In healthy subjects, the effect of single dose ketoconazole 400 mg on the kinetics of single dose (750 mg) or multiple dose (750 mg q8h) telaprevir was studied. When single

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
	significantly increased in the presence of ketoconazole: GMR AUC 9.6, Cmax 6.9.[67]	itraconazole should not exceed 200 mg/day.[1]		doses of both drugs were coadministered, telaprevir Cmax ↑ 24% and AUC ↑ 62%. However, after multiple doses of telaprevir, there was no discernible effect of ketoconazole on telaprevir exposure. High (>200 mg per day) doses of ketoconazole or itraconazole are not recommended with telaprevir.[37]
Methadone	The effect of steady-state asunaprevir 100 mg BID on the kinetics of methadone (40-120 mg daily) or buprenorphine/naloxone (8/2-24/6 mg daily) was assessed in subjects on stable opioid therapy. Asunaprevir had no clinically meaningful effect on the pharmacokinetics of methadone or buprenorphine/naloxone and was generally well-tolerated. No dose adjustment is required with coadministration.[53]	In HCV-negative volunteers on stable, maintenance doses (20-150 mg QD) of methadone, boceprevir 800 mg q8h was coadministered for 6 days. In the presence of boceprevir, exposures of R-methadone were decreased (AUC ↓ 16%, Cmax ↓ 10%) and S-methadone were decreased (AUC ↓ 22%, Cmax ↓ 17%). These changes did not result in clinically significant effects including withdrawal. Boceprevir exposures in the presence of methadone were similar to historical controls. Dose adjustment is likely not necessary when boceprevir is co-administered with methadone.[54] Clinical monitoring is recommended, with dose adjustments of methadone if	In 15 subjects on stable methadone maintenance therapy, administration of 480 mg faldaprevir (loading dose) followed by 240 mg QD faldaprevir for 7 days resulted in 11-18% ↑ in R-methadone and S-methadone exposures. There was no evidence of withdrawal as evaluated by the validated OOWS or SOWS scores. No dose adjustment is required for methadone when coadministered with faldaprevir.[55]	In HCV-negative volunteers on stable methadone maintenance therapy (median methadone dose 85 mg, range 40-120 mg/day), telaprevir 750 mg q8h was co-administered for 7 days. In the presence of telaprevir, R-methadone Cmin ↓ 31%, Cmax ↓ 21% and AUC ↓ 21%. The AUC ratio of S-/R-methadone was comparable before and during coadministration of telaprevir. The median unbound fraction of R-methadone ↑ from 7.92% to 9.98% during coadministration with telaprevir, but the median unbound Cmin of R-methadone was similar before and during telaprevir coadministration. A priori methadone dose adjustments are not required when initiating telaprevir, but close monitoring is recommended, with dose adjustments if

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		necessary during concomitant treatment with boceprevir.[1]		necessary.[68]
Midazolam	The pharmacokinetics of single dose midazolam 5 mg was assessed alone and in the presence of steady-state asunaprevir 200 mg BID in 16 healthy adult subjects. Midazolam AUC decreased 29% and Cmax decreased 21% in the presence of concomitant asunaprevir, confirming that asunaprevir is a weak CYP3A4 inducer.[4]		Healthy volunteers received an oral cocktail of probe substrates for CYP1A2, 2C9, 2C19, 2D6 and 3A4 (n=24), or efavirenz for CYP2B6 (n=14) prior to 240 mg faldaprevir BID and at faldaprevir steady state exposure. The AUC of oral midazolam (intestinal and hepatic 3A4 probe) ↑192% in the presence of faldaprevir.[10]	
NSAIDS		In healthy subjects, co-administration of diflunisal or ibuprofen (aldo ketoreductase inhibitors) had little effect on the steady-state exposure to BOC.[7]		
Oral contraceptives		In healthy subjects, there were no clinically relevant changes in BOC exposure when co-administered with drospirenone (DRSP) 3 mg/ethinyl estradiol (EE) 20 ug. BOC increased DRSP $AUC_{(0\text{-}24h)}$ and C_{max} (99% and 57%, respectively); and decreased EE AUC (24%) with no effect on EE $C_{max.}$.[7] Alternative methods of non-hormonal contraception are	In healthy female volunteers who received 30 ug ethinylestradiol (EE) and 150 ug levonorgestrel (LNG) alone or with 240 mg faldaprevir for 7 days, EE and LNG exposures were moderately higher when co-administered with faldaprevir than when administered alone.[70]	In healthy women receiving Modicon (0.5 mg norethindrone (NE) and 0.035 mg ethinyl estradiol (EE) for at least 3 months, the effect of steady-state telaprevir 750 mg q8h on the steady-state pharmacokinetics of EE and NE was assessed. In the presence of telaprevir, EE Cmax ↓ 26%, Cmin ↓ 37% and AUC ↓ 28%. NE and telaprevir exposures were not significantly affected. LH and FSH

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
		recommended. Co-administration of BOC with drospirenone (Yaz®, Yasmin®, Angeliq®) is contraindicated.[1] In healthy women, coadministration of boceprevir 800 mg TID with ethinyl estradiol (EE) 0.035 mg/norethindrone (NE)1 mg resulted in 26% ↓ AUC, 21% ↓ Cmax of EE and 17% ↓ Cmax of NE. However, based FSH, LH, SHBG, and progesterone levels, these changes are not considered clinically significant and coadministration of boceprevir with EE/NE is unlikely to alter the effectiveness of the combined oral contraceptive Ortho-Novum® 1/35.[69]		concentrations at day 7 also ↑, corresponding with the ↓ EE concentrations. **Alternative methods of contraception should be used when estrogen-based contraceptives are coadministered with telaprevir**.[71]
Pegylated interferon alfa-2b		In healthy subjects, there were no clinically relevant changes in either BOC or PEG2b exposure when co-administered with pegylated interferon alfa-2b. No BOC dosage adjustment is needed with co-administration.[7]		
Phosphodiester-ase Type 5 (PDE5) Inhibitors • **sildenafil** (Viagra®, Revatio®		↑ in PDE-5 inhibitor concentrations are expected, and may result in an increase in adverse effects, including hypotension, syncope, visual disturbances, and		↑ in PDE-5 inhibitor concentrations are expected, and may result in an increase in adverse effects. **<u>For treatment of</u>**

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
); *(CYP3A4 >>2C9 substrate ; weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 - unlikely to cause significant interactions)* • **tadalafil** (Cialis®, Adcirca®); *CYP3A4 substrate* • **vardenafil** (Levitra®); substrate of *CYP3A4 >3A5, 2C*		priapism. **<u>For treatment of pulmonary arterial hypertension (PAH):</u>**[1] • **Sildenafil or tadalafil use for PAH is contraindicated with boceprevir.** **<u>For treatment of erectile dysfunction:</u>** Use with caution and increased monitoring for PDE-5 inhibitor-associated toxicities. Do not exceed the following doses:[1] • sildenafil: 25 mg every 48 hours • tadalafil: 10 mg every 72 hours • vardenafil: 2.5 mg every 24 hours (NB: this dose not approved in Canada; therefore, combination is not recommended)		**<u>pulmonary arterial hypertension (PAH):</u>**[3] • **Sildenafil use for PAH is (contraindicated with telaprevir.** • Co-administration of tadalafil and telaprevir for PAH treatment is not recommended. **<u>For treatment of erectile dysfunction:</u>** Use with caution and increased monitoring for PDE-5 inhibitor-associated toxicities. Do not exceed the following doses:[3] • sildenafil: 25 mg every 48 hours • tadalafil: 10 mg every 72 hours • vardenafil: **contraindicated**
Proton-pump inhibitors (PPIs), including esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, etc.	The pharmacokinetics of single dose omeprazole 40 mg was assessed alone and in the presence of steady-state asunaprevir 200 mg BID in 16 healthy adult subjects. Omeprazole AUC decreased 20% and Cmax decreased 4% in the presence of concomitant asunaprevir, confirming that	In healthy volunteers administered boceprevir 800 mg TID or omeprazole 40 mg QD alone or in combination, no clinically significant changes in pharmacokinetics were noted with either drug. Boceprevir and omeprazole may be coadministered without dose adjustment.[72]	Healthy volunteers received an oral cocktail of probe substrates for CYP1A2, 2C9, 2C19, 2D6 and 3A4 (n=24), or efavirenz for CYP2B6 (n=14) prior to 240 mg faldaprevir BID and at faldaprevir steady state exposure. Omeprazole (2C19 probe) AUC ↑ 58% in the presence of faldaprevir.[10]	

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
	asunaprevir is a weak 2C19 inducer.[4]			
Ribavirin				Ribavirin pharmacokinetics were determined in 21 HCV-infected subjects, 16 on pegylated interferon/ribavirin (PR) alone, and 5 on telaprevir/PR. Dose-adjusted ribavirin plasma AUC was 1.54-fold higher in those receiving telaprevir/PR vs PR alone (p=0.002). Ribavirin mono-, di- and tri-phosphate in red blood cells were 3.3, 2.3, and 2.4-fold higher in those on telaprevir/PR compared to those on PR alone; similarly, ribavirin mono-, di- and tri-phosphate in PBMC were 2.5, 3, and 2-fold higher in those on telaprevir/PR compared to those on PR alone (all statistically significant). In patients on telaprevir/PR, intracellular ribavirin concentrations declined after stopping telaprevir. Besides telaprevir use, no other variables including Clcr, age, gender or race were associated with plasma or intracellular ribavirin pharmacokinetics. Increased ribavirin concentrations due to telaprevir coadministration may possibly be a factor in the increased rates of anemia observed with triple therapy.[73]
Rifampin	In healthy volunteers	Coadministration is		In healthy subjects,

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
	who received asunaprevir 600 mg BID alone or with multi-dose rifampin 600 mg once daily, rifampin coadministration resulted in variable effects on the pharmacokinetics of asunaprevir: GMR 0.79 (0.56-1.09) for AUC and 0.95 (0.6-1.5) Cmax. These results suggest that the induction effect of rifampin on 3A4/P-gp activity was confounded by the inhibition of liver update via OATP transporters. Hepatic exposures of asunaprevir may be decreased. Avoid coadministration of asunaprevir with strong/moderate inducers of CYP3A4 or inhibitors of OATP1B1/2 until further data are available.[67]	contraindicated, as boceprevir concentrations may be significantly reduced, possibly leading to decreased virologic response.[1]		coadministration of rifampin 600 mg daily at steady-state and single dose telaprevir 750 mg led to 86% ↓ Cmax and 92% ↓ AUC of telaprevir. Coadministration of rifampin and telaprevir is contraindicated.[37]
Warfarin		Combination has not been studied. Potential for altered warfarin concentrations in the presence of boceprevir. Monitor INR when coadministering warfarin and boceprevir.[1]	Healthy volunteers received an oral cocktail of probe substrates for CYP1A2, 2C9, 2C19, 2D6 and 3A4 (n=24), or efavirenz for CYP2B6 (n=14) prior to 240 mg faldaprevir BID and at faldaprevir steady state exposure. S-warfarin (2C9 probe) AUC ↑ 29% in the presence of faldaprevir.[10]	In vitro, the effect of 14C-telaprevir at various concentrations on the protein-binding of 3H-warfarin was evaluated in human plasma. Protein-binding of 14C-telaprevir in human plasma was 59.1-75.6% over the concentration range of 0.1 to 20 uM. The free fraction of 14C-telaprevir ↑ ~30% in the presence of warfarin at low 14C-telaprevir

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
				concentrations, but this was not observed at high 14C-telaprevir doses. Protein binding of 3H-warfarin in human plasma was 98% and was unchanged by the presence of telaprevir over the concentration range of 0.1 to 20 uM. At low 14C-telaprevir concentrations, warfarin and other ligands with high affinity binding to albumin or alpha1-acid glycoprotein may displace 14C-telaprevir from protein binding sites and ↑ the free fraction of telaprevir.[74] Case report of a 45 yo Hispanic man maintained on warfarin 6 mg daily for 8 months with therapeutic INRs (2.5-3.5). The patient initiated triple therapy with ribavirin, pegylated-interferon and telaprevir, and two days later had an INR of 6.0. He then missed five consecutive warfarin doses, resulting in a below-target INR. An increase in the weekly warfarin dose of 50% above the baseline dose (i.e., 9 mg daily) was required to re-attain a target INR. The warfarin dosing requirement began to decline only after the man finished the prescribed 12-week course of telaprevir. The warfarin dosage needed to maintain a target INR fell to nearly its baseline

	Asunaprevir (Sunvepra®, ASV, BMS-650032)	Boceprevir (Victrelis®, BOC, SCH 503034) Merck	Faldaprevir (FDV, BI201335)	Telaprevir (Incivek®, TVR, VX-950) Vertex Pharmaceuticals/ Janssen
				level after telaprevir was completed.[75] Monitor INR when coadministering warfarin and telaprevir.[3]

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

References:

1. Merck Canada Inc. Victrelis (boceprevir) Product Monograph. Kirkland, QC May 13, 2013.

2. Van Heeswijk RPG, Boogaerts G, De Paepe E, et al. The effect of different types of food on the bioavailability of the investigational HCV protease inhibitor telaprevir [abstract PK_19]. 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 22-23, 2011, Cambridge, MA.

3. Vertex Pharmaceuticals Inc. Incivek (telaprevir) Product Monograph. Laval, QC December 17, 2013.

4. Eley T, Gardiner D, Persson A, et al. Evaluation of drug interaction potential of the HCV protease inhibitor BMS-650032 at 200mg twice daily (bid) in metabolic cocktail and p-glycoprotein (p-gp) probe studies in healthy volunteers [abstract 381]. Hepatology 2011;54(S1).

5. Eley T, Han Y, Huang S, et al. In vivo and in vitro assessment of asunaprevir as an inhibitor and substrate of OATP transporters in healthy volunteers [abstract PK_04]. 7th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 27-28, 2012, Cambridge, MA.

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

7. Kasserra C, Hughes E, Treitel M, et al. Clinical pharmacology of boceprevir: metabolism, excretion, and drug-drug interactions [abstract 118]. 18th Conference on Retroviruses and Opportunistic Infections, Feb 27-Mar 2, 2011, Boston, USA.

8. Jumes P, Feng H-P, Xuan F, et al. Pharmacokinetic interaction between the HCV protease inhibitor boceprevir and digoxin in healthy adult volunteers [abstract PK_05]. 7th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 27-28, 2012, Cambridge, MA.

9. Hammond K, Wempe MF, Ray M, et al. Enzyme induction not alterations in protein binding contribute to reduced etravirine exposures with boceprevir [abstract P_21]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, May 19-21, 2014, Washington, DC.

10. Sabo J, Kashuba A, Ballow C, et al. Cytochrome P450 (CYP) interactions with the HCV protease inhibitor BI 201335 in healthy volunteers [abstract A-1248]. 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 9-12, 2012, San Francisco.

11. Cooper C, Conway B, Ghesquiere W, et al. Pharmacokinetic interactions of faldaprevir and deleobuvir (BI 207127) and their individual and combined effect on selected cytochrome P450 (CYP) probe substrates in genotype 1 hepatitis C infected patients [abstract 1083]. Hepatology 2013;58(4 suppl):732A.

12. Kunze A, Huwyler J, Camenisch G, et al. Interaction of the antiviral drug telaprevir with renal and hepatic drug transporters. Biochemical Pharmacology 2012;84:1096-102.

13. Eley T, He B, Li J, et al. Effect of hepatic impairment on the pharmacokinetics of asunaprevir (BMS-650032, ASV) [abstract]. 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), November 9-13, 2012, Boston, MA.

14. Adiwijaya B, Chandorkar G, Van Heeswijk RPG, et al. Effect of mild and moderate hepatic impairment on telaprevir pharmacokinetics [abstract PK_1]. 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 22-23, 2011, Cambridge, MA.

15. Garimella T, He B, Luo W-L, et al. Asunaprevir pharmacokinetics and safety in subjects with impaired renal function [abstract 463]. Hepatology 2013;58(4 (suppl)):430A.

16. Poland B, Kastrissios H, Gupta S, et al. Population pharmacokinetic analysis finds no clinically important effects of demographic and health covariates on boceprevir exposure [abstract PK_6]. 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 22-23, 2011, Cambridge, MA.

17. Huang F, Moschetti V, Lang B, et al. Pharmacokinetics, safety and tolerability of faldaprevir in patients with different levels of renal impairment [abstract 466]. 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), November 1-5, 2013, Washington, DC.

18. Eley T, Li W, Huang S, et al. Evaluation of pharmacokinetic drug drug interaction between BMS-791325, an NS5B non-nucleotide polymerase inhibitor, daclatasvir and asunaprevir in triple combination in HCV genotype 1 infected patients [abstract O_18]. 8th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 26-27, 2013, Cambridge, MA.

19. Bifano M, Sevinsky H, Bedford B, et al. Coadministration of BMS-790052 and BMS-650032 does not result in a clinically meaningful pharmacokinetic interaction in healthy subjects [abstract 827]. 61st Annual Meeting of the American Association for the Study of Liver Diseases, October 29-November 2, 2010, Boston, MA.

20. Bristol-Myers-Squibb. Daklinza (daclatasvir) Summary of Product Characteristics. European Union 2014.

21. Hulskotte EGJ, Feng H-P, Xuan F, et al. Pharmacokinetic interactions between the hepatitis C virus protease inhibitor boceprevir and ritonavir-boosted HIV-1 protease inhibitors atazanavir, darunavir, and lopinavir. Clin Infec Dis 2013;56(5):718-26.

22. Kiser J, Lu D, Rosenkranz S, et al. Boceprevir and antiretroviral pharmacokinetic interactions in HIV/HCV coinfected persons - AIDS clinical trials group study A5309S [abstract P_18]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, May 19-21, 2014, Washington, DC.

23. European Medicines Agency. Questions and answers on drug interactions between Victrelis (boceprevir) and ritonavir-boosted HIV protease inhibitors. 2012 February 16. Report No.: EMA/CHMP/117973/2012.

24. Garraffo R, Lavrut T, Poisot-Martin I, et al. Pharmacokinetic interactions between boceprevir and atazanavir/ritonavir or raltegravir in HIV/HCV coinfected patients [abstract O_15]. 14th International Workshop on Clinical Pharmacology of HIV Therapy, April 22-24, 2013, Amsterdam.

25. Nelson M, Arasteh K, Jain MK, et al. Effect of faldaprevir on atazanavir pharmacokinetics in patients with HIV/HCV coinfection [abstract 499]. Conference on Retroviruses and Opportunistic Infections, March 3-6, 2014, Boston, MA.

26. Van Heeswijk RPG, Vandevoorde A, Boogaerts G, et al. Pharmacokinetic interactions between ARV agents and the investigational HCV protease inhibitor TVR in healthy volunteers [abstract 119]. 18th Conference on Retroviruses and Opportunistic Infections, Feb 27-Mar 2, 2011, Boston, USA.

27. Barrail-Tran A, Braun J, Vincent C, et al. Atazanavir and ritonavir pharmacokinetics with telaprevir-based HCV treatment (ANRSHC26) [abstract MOPE42]. 20th International AIDS Conference, July 20-25, 2014, Melbourne, Australia.

28. Henshaw J, Adiwijaya B, Adda N, et al. The pharmacokinetics of telaprevir and selected ART medications in HCV/HIV co-infected patients [abstract PK_08]. 7th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 27-28, 2012, Cambridge, MA.

29. Gutierrez-Valencia A, Ruiz-Valderas R, Torres-Cornejo A, et al. Role of ritonavir in the drug interactions between telaprevir and ritonavir-boosted atazanavir. Clin Infect Dis 2014 Jan;58(2):268-73.

30. Custodio J, Guo S, Lawson EB, et al. Lack of clinically relevant drug interactions between elvitegravir plus ritonavir boosted-atazanavir and telaprevir [abstract MOPE041]. 20th International AIDS Conference, July 20-25, 2014, Melbourne, Australia.

31. Sabo J, Kort J, Ballow C, et al. Clinical assessment of potential drug interactions of faldaprevir, a hepatitis C virus protease inhibitor, with darunavir/ritonavir, efavirenz and tenofovir. Clin Infec Dis 2014;Aug 4. pii: ciu616. [Epub ahead of print].

32. Rockstroh JK, Valantin M-A, Mallolas J, et al. Pharmacokinetics of faldaprevir and antiretrovirals in patients with hiv/hcv coinfection [abstract 497]. Conference on Retroviruses and Opportunistic Infections, March 3-6, 2014, Boston, MA.

33. Bertelsen K, Montes M, Horban A, et al. Efficacy, safety and pharmacokinetics of telaprevir, peg-IFN-alfa-2a, and ribavirin in combination with darunavir/ritonavir-based HAART in HCV/HIV-1 co-infected patients (INSIGHT substudy) [abstract PE7/11]. 14th European AIDS Conference (EACS), October 16-19, 2013, Brussels, Belgium.

34. Curran A, Marti R, Lopez RM, et al. Darunavir and telaprevir drug interaction: total and unbound plasmatic concentrations in HIV-HCV coinfected patients [abstract PE10/16]. 14th European AIDS Conference (EACS), October 16-19, 2013, Brussels, Belgium.

35. Johnson M, Borland J, Chen S, et al. The effect of boceprevir and telaprevir on dolutegravir pharmacokinetics, in healthy adult subjects [abstract O_16]. 14th International Workshop on Clinical Pharmacology of HIV Therapy, April 22-24, 2013, Amsterdam.

36. ViiV Healthcare ULC. Tivicay (dolutegravir) Prescribing Information. Research Triangle Park, NC August, 2013.

37. Garg V, Chandorkar G, Yang Y, et al. The effect of CYP3A inhibitors and inducers on the pharmacokinetics of telaprevir [abstract PK_13]. 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 22-23, 2011, Cambridge, MA.

38. Custodio J, Guo S, Lawson EB, et al. Lack of clinically relevant drug Interactions between elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate and telaprevir [abstract A-1576]. 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 10-13, 2013, Denver, CO.

39. Hammond K, Wolfe P, Burton J, et al. Pharmacokinetic interaction between boceprevir and etravirine in HIV/HCV seronegative volunteers. J Acq Immune Def Syndr 2013;62(1):67-73.

40. Kakuda TN, Leopold L, Nijs S, et al. Pharmacokinetic interaction between etravirine or rilpivirine and telaprevir: a randomised, two-way crossover trial [abstract O_18]. 13th International Workshop on Clinical Pharmacology of HIV Therapy, April 16-18, 2012, Barcelona, Spain.

41. Vourvahis M, Plotka A, Kantaridis C, et al. The effects of boceprevir and telaprevir on the pharmacokinetics of maraviroc: An open-label, fixed-sequence study in healthy volunteers. J Acquir Immune Defic Syndr 2014;65(5):564-70.

42. Martel D, Sheehan NL, Tremblay CL, et al. Pharmacokinetic interaction of the directly acting antiviral agent boceprevir and maraviroc in healthy volunteers [abstract P_04]. 14th International Workshop on Clinical Pharmacology of HIV Therapy, April 22-24, 2013, Amsterdam.

43. Taburet AM, Piroth L, Paniez H, et al. Pharmacokinetics of asunaprevir, daclatasvir and raltegravir in HCV/HIV co infected patients, with or without cirrhosis, and previously null responders to pegylated interferon + ribavirin (ANRS HC30 - QUADRIH study) [abstract 1967]. American Association for the Study of Liver Diseases The Liver Meeting (AASLD), November 7-11, 2014, Boston, MA.

44. de Kanter C, Blonk M, Colbers A, et al. 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 Infec Dis 2013;56(2):300-6.

45. Moreno A, Quereda C, Montes M, et al. Safe coadministration of raltegravir-based HAART in HIV-infected patients with HCV-cirrhosis receiving triple therapy with telaprevir or boceprevir. J Acq Immune Def Syndr 2012;61(3):e47-9.

46. Joseph D, Rose P, Strelkowa N, et al. Effect of faldaprevir on raltegravir pharmacokinetics in healthy volunteers [abstract 501]. Conference on Retroviruses and Opportunistic Infections, March 3-6, 2014, Boston, MA.

47. Van Heeswijk RPG, Garg V, Boogaerts G, et al. The pharmacokinetic interaction between telaprevir and raltegravir in healthy volunteers [abstract A1-1738a]. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17-20, 2011, Chicago, IL.

48. Rhee E, Feng H-P, Xuan F, et al. Absence of a significant pharmacokinetic interaction between the hepatitis C virus protease inhibitor boceprevir and HIV-1 NNRTI rilpivirine [abstract 537]. 20th Conference on Retroviruses and Opportunistic Infections, March 3-6, 2013, Atlanta, GA.

49. Kempf DJ, Klein C, Chen HJ, 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.

50. Garg V, Luo X, McNair L, et al. Low-dose ritonavir and the pharmacokinetics of the investigational HCV protease inhibitor telaprevir in healthy volunteers [abstract 629]. 18th Conference on Retroviruses and Opportunistic Infections, Feb 27-Mar 2, 2011, Boston, USA.

51. Van Heeswijk R, Gysen V, Googaerts G, et al. The pharmacokinetic interaction between tenofovir disoproxil fumarate and the investigational HCV protease inhibitor telaprevir [abstract A-966]. 48th Interscience Conference on Antimicrobial Agents and Chemotherapy, October 25-28, 2008, Washington, DC.

52. Lee JE, Van Heeswijk RPG, Alves K, et al. Effect of the hepatitis C virus protease inhibitor telaprevir on the pharmacokinetics of amlodipine and atorvastatin. Antimicrob Agents Chemother 2011;55(10):4569-74.

53. Garimella T, Eley T, He B, et al. Evaluation of drug-drug interaction between asunaprevir and methadone or buprenorphine/naloxone [abstract 823]. ID Week 2014, October 8-12, 2014, Philadelphia, PA.

54. Hulskotte EGJ, Feng H-P, Bruce RD, et al. Pharmacokinetic interaction between HCV protease inhibitor boceprevir and methadone or buprenorphine in subjects on stable maintenance therapy [abstract PK_09]. 7th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 27-28, 2012, Cambridge, MA.

55. Joseph D, Schobelock M, Riesenberg RA, et al. Effect of steady-state faldaprevir on the pharmacokinetics of steady-state methadone and buprenorphine/naloxone in subjects on stable addiction management therapy [abstract 483]. Hepatology 2013;58(4 (suppl)):440A.

56. Luo X, Trevejo J, Van Heeswijk RPG, et al. Effect of telaprevir on the pharmacokinetics of buprenorphine in volunteers on stable buprenorphine/naloxone maintenance therapy. Antimicrob Agents Chemother 2012;56(7):3641-7.

57. Foisy MM, Yakiwchuk EMK, Chiu I, et al. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV Med 2008;9(6):389-96.

58. Jumes P, Feng H-P, Chatterjee M, et al. Pharmacokinetic interaction between the hepatitis C virus protease inhibitor boceprevir and prednisone in healthy volunteers [abstract 1896]. 63rd Annual Meeting of the American Association for the Study of Liver Diseases, November 9-13, 2012, Boston, MA.

59. Garimella T, Adamczyk R, Stonier M, et al. Effect of steady state daclatasvir plus asunaprevir on the single dose pharmacokinetics of the p-glycoprotein substrate digoxin in healthy adult subjects [abstract 822]. ID Week 2014, October 8-12, 2014, Philadelphia, PA.

60. Garg V, Chandorkar G, Farmer HF, et al. Effect of telaprevir on the pharmacokinetics of midazolam and digoxin. J Clin Pharmacol 2012;52(10):1566-73.

61. Wire MB, Fang L, Hussaini A, et al. Lack of Clinically Significant Pharmacokinetic Interaction between the Thrombopoietin Receptor Agonist Eltrombopag and Hepatitis C Virus Protease Inhibitors Boceprevir and Telaprevir. Antimicrob Agents Chemother 2014 Nov;58(11):6704-9.

62. Garimella T, Adamczyk R, Hu P, et al. No clinically-relevant interactions between asunaprevir and selective serotonin reuptake inhibitors (escitalopram and sertraline) in healthy subjects [abstract 493]. Hepatology 2013;58(4 suppl):445A.

63. Hulskotte EGJ, Gupta S, Xuan F, et al. Coadministration of the HCV protease inhibitor boceprevir has no clinically meaningful effect on the pharmacokinetics of the selective serotonin reuptake inhibitor escitalopram in healthy volunteers [abstract]. HEP DART, December 4-8, 2011, Koloa, Hawaii.

64. Van Heeswijk RPG, Boogaerts G, De Paepe E, et al. The pharmacokinetic interaction between escitalopram and the investigational HCV protease inhibitor telaprevir [abstract 12]. 5th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 23-24, 2010, Boston, MA.

65. Hulskotte EGJ, Feng H-P, Xuan F, et al. Pharmacokinetic evaluation of the interaction between the HCV protease inhibitor boceprevir and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and pravastatin. Antimicrob Agents Chemother 2013;57:2582-8.

66. U.S. Food and Drug Administration. HIV/AIDS Update - Important info about interactions between certain HIV drugs and cholesterol-lowering statin drugs. March 1, 2012.

67. Eley T, He B, Huang S, et al. Effect of multiple dose ketoconazole and the effect of multiple dose rifampin on pharmacokinetics of the HCV NS3 protease inhibitor asunaprevir [abstract O_13]. 8th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 26-27, 2013, Cambridge, MA.

68. Van Heeswijk RPG, Verboven P, Vandevoorde A, et al. Pharmacokinetic interaction between telaprevir and methadone. Antimicrob Agents Chemother 2013;57:2304-9.

69. Lin WH, Feng H-P, Chatterjee M, et al. Pharmacokinetic interaction between the hepatitis C virus protease inhibitor boceprevir and ethinyl estradiol/norethindrone [abstract 1901]. 63rd Annual Meeting of the American Association for the Study of Liver Diseases, November 9-13, 2012, Boston, MA.

70. Sabo J, Lang B, Elgadi M, et al. Effect of multiple oral doses of faldaprevir on the multiple dose pharmacokinetics of a combination oral tablet of ethinylestradiol and levonorgestrel in healthy premenopausal female volunteers [abstract 482]. Hepatology 2013;58(4 (suppl)):440A.

71. Garg V, Van Heeswijk RPG, 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(10):1574-83.

72. De Kanter C, Colbers A, Blonk M, et al. Lack of a clinically significant drug-drug interaction in healthy volunteers between the HCV protease inhibitor boceprevir and the proton pump inhibitor omeprazole. J Antimicrob Chemother 2013;68(6):1415-22.

73. Hammond K, Jimmerson L, MacBrayne CE, et al. Increased plasma intracellular ribavirin concentrations associated with telaprevir use [abstract PP_02]. 14th International Workshop on Clinical Pharmacology of HIV Therapy, April 22-24, 2013, Amsterdam.

74. Chakilam A, Chavan A, Smith G, et al. Telaprevir binding to isolated human plasma proteins and protein binding displacement interactions between telaprevir and ritonavir or warfarin [abstract PK_20]. 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 22-23, 2011, Cambridge, MA.

75. Gatti DC, Cha A. Apparent interaction between telaprevir and warfarin in a patient with chronic hepatitis C viral infection. . Am J Health Syst Pharm 2012;69(23):2062-5.