DRUG INTERACTIONS WITH NEW/INVESTIGATIONAL HEPATITIS C NS5A INHIBITORS

	Daclatasvir (Daklinza®, DCV, BMS-790052) ***Bristol-Myers Squibb***	**Ledipasvir (LDV, GS-5885)** ***Gilead***	**Elbasvir (MK-8742)** ***Merck***	**Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267)** ***Abbvie***
Pharmacology	NS5A replication complex inhibitor	NS5A inhibitor	NS5A inhibitor	NS5A inhibitor
Adult Dose	*Approved in Japan and the EU:* 60 mg once daily	90 mg once daily Coformulated with sofosbuvir 400 mg in a fixed dose tablet (Harvoni®).	*Investigational:* 50 mg once daily Coformulated with grazoprevir (MK-5172) in a fixed dose tablet.	25 mg once daily Co-formulated as 12.5 mg ombitasvir/75 mg paritaprevir/50 mg ritonavir tablet (daily dose is 2 tablets once daily).
Impact of Food	No food effect.	No impact of moderate-fat or high-fat meal vs fasting on ledipasvir pharmacokinetics. Ledipasvir/sofosbuvir may be taken with or without food.[1]		Take with food.
Kinetic Characteristics	Substrate of CYP3A4 and substrate and inhibitor of P-gp. Inhibitor of OATP1B1, OCT1, and BCRP.[2] Approximately 2/3 excreted unchanged in bile.	Primarily excreted (>98%) unchanged in the feces, with little renal excretion.[3] Not an inhibitor or inducer of P450 or UGT. Likely a substrate of P-gp. Weak inhibitor of P-gp and BRCP (intestinal, not systemic). Likely a weak inhibitor of OATP1B1/1B3.[4] Variables such as age, body weight, gender, race, cirrhosis, ribavirin usage, and disease status do not have a clinically relevant impact on ledipasvir exposures in HCV-infected subjects.[5]	Substrate of CYP3A4, P-glycoprotein (P-gp) and the organic anion-transporting polypeptide (OATP) in vitro. No age effect observed in young (22-45 yrs) vs elderly (65-78 yrs) males; ~33% higher AUC in elderly female vs male subjects after adjusting for body weight.[6]	Substrate of 3A4, P-gp, BCRP. Inhibits UGT1A1.[7]
Effect of hepatic impairment	In an open-label, parallel-group study of daclatasvir in subjects without	The kinetics of single and multiple-dose ledipasvir were evaluated in HCV-	In adult cirrhotic patients with either Child-Pugh A (n=8) or Child-Pugh B	The pharmacokinetics of single-dose paritaprevir 200

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	active HCV with mild, moderate, or severe hepatic impairment (Child Pugh A, B, C, respectively), total daclatasvir drug exposures were lower versus healthy controls. Total daclatasvir exposures were similar to those observed in HCV-infected subjects in a previous study. Subjects with moderate or severe hepatic impairment and HCV-infected patients demonstrated a higher unbound fraction compared to healthy controls; thus, active unbound daclatasvir exposures were similar to controls. Daclatasvir dose adjustments are not required in hepatic failure.[8]	uninfected subjects with moderate (Child Pugh class B) or severe hepatic (Child Pugh class C) impairment. No clinically relevant changes in ledipasvir AUC were observed in moderate or severe hepatic impairment compared to matched subjects with normal hepatic function. Ledipasvir Cmax ↓ 36% and t1/2 was modestly prolonged in subjects with severe hepatic impairment, possibly due to lower absorption/bioavailability and reduced clearance. There was no effect of severe hepatic impairment on ledipasvir plasma protein binding. Study drugs were well tolerated. Dose adjustment of ledipasvir in patients with mild, moderate, or severe hepatic impairment is not required.[9]	(n=7), single 50 mg oral doses of MK-8742 resulted in ↓ 24% AUC, 42% ↓ Cmax and 27% ↓ C24h in mild hepatic impairment and ↓ 14% AUC, 31% ↓ Cmax and 17% ↓ C24h in moderate hepatic impairment compared to historical healthy controls. These results are not clinically meaningful and support the administration of MK-8742 to patients with mild and moderate hepatic dysfunction.[10]	mg/ritonavir 100 mg/ ombitasvir 25 mg and dasabuvir 400 mg were assessed in in subjects with mild, moderate, or severe hepatic impairment and compared to healthy controls. In subjects (n=6) with **mild hepatic impairment (Child-Pugh A)**, AUC of ombitasvir was comparable (8% lower) to subjects with normal hepatic function • In subjects (n=6) with **moderate hepatic impairment (Child-Pugh B)**, AUC of ombitasvir was 30% lower than subjects with normal hepatic function. • In subjects(n=5) with **severe hepatic impairment (Child-Pugh C)**, AUC of ombitasvir and was 55% lower compared to subjects with normal hepatic function. No dose adjustment is required for the 3D regimen in subjects with mild hepatic impairment (Child Pugh A).[11]
Effect of renal impairment	The pharmacokinetics of single dose daclatasvir 60 mg were assessed in 12 HCV-negative subjects with end-	No dosage adjustment is required for patients with mild, moderate or severe renal impairment.[13]		The single dose pharmacokinetics of ombitasvir, paritaprevir, ritonavir and dasabuvir were evaluated in non-HCV infected

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	stage renal disease (eGFR<15 mL/min/1.73 m2) and in 12 subjects with normal renal function. The total and unbound AUC of daclatasvir were increased 1.8- and 1.5-fold, respectively in subjects with severe renal impairment compared to subjects with normal renal function. The increase in daclatasvir exposure was within exposures observed in population PK. A correlation between higher exposures and adverse events has not been shown.[12] Dose adjustment of daclatasvir in renal impairment is not required.[2]	Safety and efficacy have not been established in patients with ESRD requiring hemodialysis, and no dosage recommendation can be given for patients with ESRD.[14]		subjects with varying degrees of renal impairment: • Mild renal impairment (Clcr 60-89 mL/min): paritaprevir, ritonavir and dasabuvir AUC values increased by 19%, 42% and 21%, respectively, while ombitasvir AUC values were unchanged relative to subjects with normal renal function. • Moderate renal impairment (CLcr: 30 to 59 mL/min): paritaprevir, ritonavir and dasabuvir AUC values increased by 33%, 80% and 37%, respectively, while ombitasvir AUC values were unchanged relative to subjects with normal renal function. • Severe renal impairment (CLcr: 15 to 29 mL/min): paritaprevir, ritonavir and dasabuvir AUC values increased by 45%, 114% and 50%, respectively, while ombitasvir AUC values were

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
				unchanged relative to subjects with normal renal function. Changes in exposure of ombitasvir, paritaprevir, ritonavir and dasabuvir in non-HCV infected subjects with mild-, moderate- and severe renal impairment are not expected to be clinically relevant. No data are available on the use of Viekira Pak in non-HCV infected subjects with End Stage Renal Disease (ESRD).[7]
Directly Acting Antivirals:				
Asunaprevir	No clinically meaningful interaction observed in healthy volunteers.[15]			
Asunaprevir + BMS-791325 (non-nucleoside inhibitor of NS5B)	In a phase 2a open-label multi-dose study, HCV-infected subjects received daclatasvir 60 mg daily with asunaprevir 200 mg BID and BMS-791325 75 mg or 150 mg BID for 12 or 24 weeks. Daclatasvir exposures were similar to historical controls, while asunaprevir exposures were ↓ ~30% but variability was high. No			

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	**Ledipasvir (LDV, GS-5885) *Gilead***	**Elbasvir (MK-8742) *Merck***	**Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie***
	dosing adjustments are required when using this triple combination.[16]			
Boceprevir	Potential for increased daclatasvir exposures due to CYP3A4 inhibition by boceprevir. Reduce daclatasvir dose to 30 mg once daily when coadministered with boceprevir or other strong inhibitors of CYP3A4.[2]			
Grazoprevir (MK-5172, NS3/4A protease inhibitor)	In an open-label, fixed-sequence, multiple-dose study, healthy subjects received 60 mg daclatasvir once daily for 7 days followed by a 4 day washout, then 200 mg MK-5172 once daily for 7 days, followed by the combination of 200 mg MK-5172 and 60 mg daclatasvir daily for 8 days. The steady-state kinetics of both daclatasvir and MK-5172 were not significantly altered when coadministered. Dose adjustments are not required with this combination.[17]			
Simeprevir	With coadministration of simeprevir 150 mg daily and daclatasvir 60 mg daily, daclatasvir AUC increased	Concentrations of ledipasvir and simeprevir are increased with coadministration. Coadministration is not recommended.[14]		

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	96%, Cmax increased 50%, Cmin increased 168%, and simeprevir AUC increased 44%, Cmax increased 39% and Cmin increased 49% compared to either drug administered alone. No dose adjustment of daclatasvir or simeprevir are required with coadministration.[2]			
Sofosbuvir (NS5B nucleotide inhibitor)	In an open-label randomized PK substudy in HCV-infected patients, subjects received sofosbuvir 400 mg QD for 7 days before initiation of daclatasvir 60 mg QD for a total of 24 weeks. Exposures of the sofosbuvir metabolite GW-331007 were similar in the presence and absence of daclatasvir, while sofosbuvir exposures were approximately 35% ↑ in the presence of daclastasvir. Daclatasvir exposures were similar to historical controls. These findings suggest the absence of a clinically relevant interaction between daclatasvir and sofosbuvir.[18] No dose adjustment of	In an open-label, fixed-sequence, cross-over study in healthy volunteers, no clinically significant interactions were observed between sofosbuvir 400 mg and either ledipasvir 90 mg QD, GS-9669 500 mg QD, or the combination of ledipasvir with GS-9669. Sofosbuvir AUC was ↑ 2.3-fold by ledipasvir, ↑ 1.4-fold by GS-9669, and ↑ 3-fold by ledipasvir and GS-9669, which corresponded to increases in total drug-related material of 26%, 15% and 40%, respectively. These changes were not considered clinically significant, and the pharmacokinetics of the circulating metabolite GS-331007 were unaffected. Similarly,		

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	daclatasvir and sofosbuvir are required with coadministration.[2]	the pharmacokinetics of ledipasvir and GS-9669 were unaffected by coadministration of sofosbuvir. No dose adjustment of sofosbuvir, ledipasvir, or GS-9669 is required with coadministration.[19]		
Telaprevir	With coadministration of telaprevir 750 mg q8h and daclatasvir 20 mg daily, daclatasvir AUC increased 115%, Cmax 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.[2]			
Antiretrovirals:				
Atazanavir/ritonavir	In an exploratory, open-label study, healthy subjects received daclatasvir 60 mg daily alone for 4 days followed by daclatasvir 20 mg daily with atazanavir 300/ritonavir 100 mg daily for 10 days. Dose-normalized changes in daclatasvir Cmax and AUC (35% ↑ and 110% ↑, respectively), were below predicted	In healthy volunteers, coadministration of ledipasvir/sofosbuvir with either atazanavir 300/ritonavir 100 mg plus tenofovir/FTC or darunavir 800/ritonavir 100 mg plus tenofovir/FTC resulted in moderate (40-60%) increases in tenofovir exposures compared to tenofovir concentrations with boosted PIs in the absence of ledipasvir/sofosbuvir.[21]	In an open-label, 3 period study, healthy subjects received MK-8742 50 mg once daily for 14 days. After a 7 day washout, subjects received atazanavir/ritonavir 300/100 mg daily for 14 days, followed by coadministration of MK-8742 50 mg daily plus ATV/r daily for 7 days. MK-8742 did not significantly impact ATV exposures	In 24 healthy subjects, the impact of atazanavir 300 mg once daily on the kinetics of AbbVie's 3D regimen (paritaprevir/ritonavir/ ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) was investigated. In the presence of atazanavir, paritaprevir AUC increased 94%, Cmax increased 46% and C24 increased 226%, likely

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	estimations. Atazanavir/ritonavir concentrations were similar to historical data.[20] Reduce daclatasvir dose to 30 mg once daily when coadministered with atazanavir/ritonavir or other strong inhibitors of CYP3A4.[2]	<u>When using tenofovir with a ritonavir- or cobicistat-boosted regimen</u>: The Canadian Harvoni® product monograph recommends monitoring for tenofovir-associated adverse reactions.[22] In contrast, the U.S. Harvoni® product monograph recommends considering alternative HCV or HIV therapy due to potential increases in tenofovir exposures.[14, 22]	(atazanavir AUC GMR of 1.07). MK-8742 exposure was significantly increased in the presence of ATV/r (MK-8742 AUC GMR 4.76 [4.07, 5.56]. This increase is postulated to be secondary to CYP3A4/Pgp inhibition by ATV/r and potential inhibition of OATP-mediated disposition of MK-8742.[23]	secondary to inhibition of OATP1B1/B3. Ombitasvir AUC was decreased 17%, Cmax decreased 23% and C24 decreased 11%, while dasabuvir AUC decreased 18%, Cmax decreased 17% and C24 decreased 21% in the presence of atazanavir. Exposures of paritaprevir greater than 2-fold were safe and well tolerated in phase 2 studies. No dose adjustments for paritaprevir/ritonavir, ombitasvir and dasabuvir or atazanavir are required when coadministered.[24]
Darunavir/ritonavir	Daclatasvir AUC increased 41%, Cmax decreased 23% when coadministered with darunavir/ritonavir. No dose modifications required when coadministering daclatasvir with darunavir/ritonavir or darunavir/cobicistat.[25]	In healthy volunteers, coadministration of ledipasvir/sofosbuvir with either atazanavir 300/ritonavir 100 mg plus tenofovir/FTC or darunavir 800/ritonavir 100 mg plus tenofovir/FTC resulted in moderate (40-60%) increases in tenofovir exposures compared to tenofovir concentrations with boosted PIs in the absence of ledipasvir/sofosbuvir.[21] <u>When using tenofovir with a ritonavir- or</u>	In an open-label, 3 period study, healthy subjects received MK-8742 50 mg once daily for 14 days. After a 7 day washout, subjects received darunavir/ritonavir 600/100 mg BID for 14 days, followed by coadministration of MK-8742 50 mg daily plus DRV/r BID for 7 days. MK-8742 did not significantly impact DRV exposures (darunavir AUC GMR of 0.95). MK-8742 exposure was	In healthy subjects, potential interactions were evaluated between AbbVie's 3D regimen (paritaprevir/ritonavir/ ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) and darunavir 800 mg once daily or 600 mg/100 mg BID (2nd darunavir dose administered with additional ritonavir). With coadministration, darunavir Cmax and AUC were not significantly affected, but darunavir

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
		cobicistat-boosted regimen: The Canadian Harvoni® product monograph recommends monitoring for tenofovir-associated adverse reactions.[22] In contrast, the U.S. Harvoni® product monograph recommends considering alternative HCV or HIV therapy due to potential increases in tenofovir exposures.[14, 22]	significantly increased in the presence of ATV/r (MK-8742 AUC GMR 1.66 [1.35, 2.05]. This increase is postulated to be secondary to CYP3A4/Pgp inhibition by DRV/r and potential inhibition of OATP-mediated disposition of MK-8742.[23]	Ctroughs were 43-48% lower. With darunavir 800 mg plus the 3D regimen, darunavir Cmax decreased 8%, AUC decreased 24% and Ctrough decreased 48%, paritaprevir Cmax increased 54%, AUC increased 29% and Ctrough increased 30%, dasabuvir Cmax increased 10%, AUC decreased 6% and Ctrough decreased 10%, ombitasvir Cmax and AUC decreased 14% and Ctrough decreased 13%.[24] With darunavir 600 mg BID, darunavir Cmax decreased 13%, AUC decreased 20% and Ctrough decreased 43%, paritaprevir Cmax decreased 30%, AUC decreased 41% and Ctrough decreased 17%, dasabuvir Cmax decreased 16%, AUC decreased 27%, Ctrough decreased 46%, ombitasvir Cmax decreased 24% and AUC and Ctrough decreased 27%.[24] No dose adjustments for paritaprevir/ritonavir, ombitasvir, dasabuvir

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
				and darunavir once or twice daily are required when coadministered.[24]
Dolutegravir	In healthy volunteers, coadministration of dolutegravir 50 mg daily and daclatasvir 60 mg daily for 5 days led to increased dolutegravir exposures (33% increase AUC, 29% increase Cmax and 45% increase Ctau) compared to dolutegravir 50 mg administered alone. These changes are not considered clinically significant. Daclatasvir exposures were not impacted by coadministration with dolutegravir.[26] Combination may be coadministered without dose adjustment.[2]	In healthy subjects, coadministration of dolutegravir 50 mg daily and tenofovir 300 mg/emtricitabine 200 mg daily with ledipasvir/sofosbuvir daily for 10 days did not result in any significant changes in the pharmacokinetics of ledipasvir, sofosbuvir, dolutegravir or emtricitabine. Tenofovir exposures were 61-115% higher with coadministration. Ledipasvir/sofosbuvir may be coadministered with dolutegravir. If tenofovir/emtricitabine is included as an NRTI backbone, appropriate monitoring for tenofovir-associated toxicities is recommended.[27]	In healthy volunteers, when single dose dolutegravir 50 mg was administered alone or in the presence of steady state grazoprevir 200/elbasvir 50 mg once daily, neither dolutegravir nor elbasvir pharmacokinetics were significantly impacted with coadministration. Dose adjustments are not required.[28]	
Efavirenz	In an exploratory, open-label study, healthy subjects received daclatasvir 60 mg daily alone for 4 days followed by efavirenz 600 mg daily first with daclatasvir 60 mg daily for 9 days, then with daclatasvir 120 mg daily for 5 days. Dose-normalized changes in daclatasvir Cmax	In a multi-dose, randomized, cross-over study, healthy volunteers (n=32) received ledipasvir/sofosbuvir 90/400 mg QD alone followed by coadministration with efavirenz/tenofovir/FTC (Atripla®) QD or Atripla® alone followed by coadministration with ledipasvir/sofosbuvir for 14 days. A	In an open-label, fixed sequence study, 10 healthy subjects received MK-8742 50 mg once daily for 7 days followed by a 7-day washout, EFV 600 mg once daily for 14 days, and then 50 mg MK-8742 and 600 mg EFV coadministered once daily for 7 days. In the presence of steady-state EFV,	In healthy subjects, potential interactions were evaluated between paritaprevir/ritonavir 150/100 mg QD and dasabuvir 400 mg BID and efavirenz 600/tenofovir 300/emtricitabine 200 mg (Atripla) once daily. This study was prematurely discontinued due to adverse events (primarily

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	and AUC (17% ↓ and 32% ↓, respectively), were below predicted estimations. Efavirenz trough concentrations were unchanged from day 11 onward.[20] Increase daclatasvir dose to 90 mg once daily with efavirenz.[2]	modest decrease (34%) in LDV exposure was noted with Atripla® co-administration, with no impact on sofosbuvir or GS-331007 pharmacokinetics. This change was not considered clinically relevant. Tenofovir plasma concentrations increased 1.8-2.6-fold in the presence of ledipasvir/sofosbuvir. The overall tenofovir AUCs were comparable to those obtained when tenofovir/FTC is coadministered with boosted HIV protease inhibitors, and dose adjustment is not warranted. Ledipasvir/sofosbuvir may be coadministered with efavirenz with a backbone of tenofovir/FTC.[29] Monitor for tenofovir-associated adverse reactions.[14]	MK-8742 AUC was decreased 54%, likely due to CYP3A4 induction by EFV. Efavirenz exposures were not significantly impacted when coadministered with MK-8742 (efavirenz AUC decreased 18%).[30]	neurological, gastrointestinal, ALT/AST elevations) in several subjects. Coadministration of efavirenz and the 3D regimen is **contraindicated** due to increased frequency of adverse events.[31]
Elvitegravir/ cobicistat	Potential for increased daclatasvir exposures due to CYP3A4 inhibition by cobicistat. Reduce daclatasvir dose to 30 mg once daily when coadministered with cobicistat or other strong inhibitors of CYP3A4.[2]	Potential for increased tenofovir exposures. The Canadian Harvoni® product monograph recommends monitoring for tenofovir-associated toxicity,[22] while the US Harvoni® monograph states that coadministration		

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
		is not recommended.[14] In healthy subjects, coadministration of **elvitegravir/cobicistat/ FTC/tenofovir alafenamide** plus ledipasvir/sofosbuvir for 10 days resulted in 65-93% increase in ledipasvir exposures, 47% increase in sofosbuvir AUC, 48% increase in GS-331007 AUC, 46% increase in elvitegravir Ctau and 53% and 225% increase in cobicistat AUC and Ctau, respectively. These changes are not considered clinically relevant. No changes in FTC, tenofovir alafenamide or tenofovir pharmacokinetics were observed with coadministration. Combination may be coadministered.[27]		
Etravirine	Potential for decreased daclatasvir exposures due to CYP3A4 induction by etravirine. Due to lack of data, coadministration of daclatasvir with etravirine is not recommended.[2]			
Lopinavir/ritonavir	Daclatasvir AUC increased 15%, Cmax decreased 33% when coadministered with	Potential for increased tenofovir exposures when coadministered with regimens including	In an open-label, 3 period study, healthy subjects received MK-8742 50 mg once daily for 14 days.	In healthy subjects, potential interactions were evaluated between AbbVie's 3D regimen

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	lopinavir/ritonavir. No dose modifications required when coadministering daclatasvir with lopinavir/ritonavir.[25]	tenofovir plus a ritonavir-boosted protease inhibitor. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions.[14]	After a 7 day washout, subjects received lopinavir/ritonavir 400/100 mg BID for 14 days, followed by coadministration of MK-8742 50 mg daily plus LPV/r BID for 7 days. MK-8742 did not significantly impact LPV exposures (lopinavir AUC GMR of 1.02). MK-8742 exposure was significantly increased in the presence of LPV/r (MK-8742 AUC GMR 3.71 [3.05, 4.53]. This increase is postulated to be secondary to CYP3A4/Pgp inhibition by LPV/r and potential inhibition of OATP-mediated disposition of MK-8742.[23]	(paritaprevir/ritonavir/ ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) and lopinavir/ritonavir 400/100 mg BID or 800/200 mg QD. With coadministration, lopinavir Ctrough was 218% higher when administered once daily in the evening. Lopinavir Cmax, AUC, and Ctrough were otherwise not significantly impacted in the presence of the 3D regimen. With lopinavir 800/ritonavir 200 mg plus the 3D regimen, lopinavir Ctrough was increased 218%, paritaprevir Ctrough increased 8.23-fold and AUC increased 87%, dasabuvir Cmax decreased 64%, AUC decreased 66%, Ctrough decreased 53%, and ombitasvir Cmax decreased 87%, AUC decreased 3% and Ctrough increased 24%.[24] With lopinavir 400/ritonavir 100 mg BID plus the 3D regimen, lopinavir Cmax decreased 13%, AUC decreased 6%, Ctrough increased 15%, paritaprevir exposures increased

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
				2-fold, dasabuvir Ctrough decreased 32% and AUC and Cmax were unchanged, and ombitasvir Cmax increased 14%, AUC increased 17% and Ctrough increased 17%.[24] Coadministration of paritaprevir/ritonavir, ombitasvir and dasabuvir with lopinavir/ritonavir once or twice daily is **not recommended** due to higher incidence of gastrointestinal adverse effects and higher ABT-450 exposures (lopinavir Ctrough increased 218% when dosed once daily with 3D regimen).[24]
Maraviroc	Clinically significant interaction not expected. Combination may be coadministered without dose adjustment.[2]			
Nevirapine	Potential for decreased daclatasvir exposures due to CYP3A4 induction by nevirapine. Due to lack of data, coadministration of daclatasvir with nevirapine is not recommended.[2]			
Raltegravir	Clinically significant interaction not expected. Combination may be coadministered	In a multi-dose, randomized, cross-over study, healthy volunteers (n=30) received ledipasvir	In an open-label, fixed sequence study, 10 subjects received a single dose of 400 mg RAL	In healthy subjects, potential interactions were evaluated between AbbVie's 3D regimen

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	without dose adjustment.[2] Clinically significant pharmacokinetic interaction not observed in 20 HIV/HCV coinfected subjects on raltegravir-based therapy who received combination therapy with pegylated interferon, ribavirin, asunaprevir 100 mg BID and daclatasvir 60 mg daily.[32]	90 mg QD, raltegravir 400 mg BID and ledipasvir plus raltegravir each for 10 days. Ledipasvir pharmacokinetics were unaffected with raltegravir co-administration. Small changes (<20%) in raltegravir were observed when coadministered with ledipasvir, but these changes were not considered clinically relevant. Ledipasvir and ledipasvir/sofosbuvir may be coadministered with raltegravir with a backbone of tenofovir/FTC.[29]	followed by a 4-day washout, a single dose of 50 mg MK-8742 followed by a 7-day washout, and then a single dose of 400 mg raltegravir coadministered with a single dose of 50 mg MK-8742. Exposures of both MK-8742 and RAL were not significantly altered when coadministered (RAL AUC GMR 1.02, MK-8742 GMR 0.81).[30]	(paritaprevir/ritonavir/ ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) and raltegravir 400 mg BID. With coadministration, raltegravir pharmacokinetics were 100-134% higher while pharmacokinetics of the 3D regimen were unchanged. No dose adjustment is recommended when raltegravir and the 3D regimen are coadministered.[7, 31]
Rilpivirine	Clinically significant interaction not expected. Combination may be coadministered without dose adjustment.[2]	In a multi-dose, randomized, cross-over study, healthy volunteers (n=32) received ledipasvir/sofosbuvir 90/400 mg QD alone followed by coadministration with rilpivirine/tenofovir/FTC (Complera®) QD or Complera® alone followed by coadministration with ledipasvir/sofosbuvir for 10 days. Ledipasvir and sofosbuvir pharmacokinetics were unaffected with Complera® co-administration. Tenofovir plasma concentrations increased 1.3-1.9-fold in the presence of		In healthy subjects, potential interactions were evaluated between AbbVie's 3D regimen (paritaprevir/ritonavir/ ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) and rilpivirine 25 mg daily. With coadministration, rilpivirine pharmacokinetics were 116-273% higher, paritaprevir exposures were minimally affected (+/- 32%) and ombitasvir and dasabuvir pharmacokinetics were unchanged. Coadministration of rilpivirine with the 3D

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
		ledipasvir/sofosbuvir. The overall tenofovir AUCs were comparable to those obtained when tenofovir/FTC is coadministered with boosted HIV protease inhibitors, and dose adjustment is not warranted. Ledipasvir/sofosbuvir may be coadministered with rilpivirine with a backbone of tenofovir/FTC.[29]		regimen is **not recommended,** as increased rilpivirine exposures may be associated with increased risk of QTc prolongation.[31]
Tenofovir	In an exploratory, open-label crossover study, healthy subjects received daclatasvir 60 mg daily, tenofovir 300 mg once daily, or both for 7 days. Cmax and AUC exposures of daclatasvir and tenofovir were similar when coadministered vs when given alone. No dose adjustment is required with coadministration.[20]	In healthy volunteers, coadministration of ledipasvir/sofosbuvir with either Atripla® (efavirenz/tenofovir/ emtricitabine) or Complera® (rilpivirine/tenofovir/ emtricitabine) resulted in increased tenofovir exposures 1.8-2.6-fold and 1.3-1.9-fold, respectively.[29] These overall tenofovir AUCs were comparable to those obtained when tenofovir/FTC is coadministered with boosted HIV protease inhibitors, and dose adjustment is not warranted. In healthy volunteers, coadministration of ledipasvir/sofosbuvir with either atazanavir 300/ritonavir 100 mg plus tenofovir/FTC or darunavir 800/ritonavir 100 mg plus tenofovir/FTC	In an open-label, fixed sequence study, 10 healthy subjects received tenofovir 300 mg once daily for 7 days followed by a 7-day washout, 50 mg MK-8742 once daily for 8 days, then 50 mg MK-8742 and tenofovir 300 mg coadministered once daily for 7 days. Tenofovir AUC was increased 34% in the presence of MK-8742, while MK-8742 exposures were not significantly altered with coadministration (MK-8742 AUC decreased 7%). This interaction is not considered clinically meaningful.[30]	The pharmacokinetics of AbbVie's 3D regimen (paritaprevir/ritonavir/ ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) regimen with and without emtricitabine 200 mg and tenofovir 300 mg once daily was assessed in healthy volunteers. The DAAs showed a minimal impact on tenofovir pharmacokinetics (tenofovir AUC increased 13%, Cmax increased 7%, Ctrough increased 24%).[33]

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
		resulted in moderate (40-60%) increases in tenofovir exposures compared to tenofovir concentrations with boosted PIs in the absence of ledipasvir/sofosbuvir.[21] <u>When using tenofovir with a ritonavir- or cobicistat-boosted regimen</u>: The Canadian Harvoni® product monograph recommends monitoring for tenofovir-associated adverse reactions.[22] In contrast, the U.S. Harvoni® product monograph recommends considering alternative HCV or HIV therapy due to potential increases in tenofovir exposures.[14, 22]		
Other Drugs:				
Acid reducing agents (H2RA and proton pump inhibitors) **equivalent doses:* *<u>PPIs (daily standard dose):</u>* *Esomeprazole 20 mg* *Lansoprazole 30 mg* *Omeprazole 20 mg* *Pantoprazole 40 mg* *Rabeprazole 20 mg* *<u>H2RAs (treatment)</u>:* *Famotidine 20 mg BID or 40 mg qhs* *Nizatidine 150 mg*	With coadministration of single dose **famotidine 40 mg** and single dose daclatasvir 60 mg, daclatasvir AUC decreased 18%, Cmax decreased 44% and Cmin decreased 11%. These changes are not considered clinically significant and dose adjustment of	In healthy subjects, fixed dose ledipasvir/sofosbuvir 90/400 mg was administered simultaneously then 12 hours after **famotidine 40 mg**. Coadministration of famotidine (simultaneous or staggered) lowered ledipasvir Cmax 17-20% without altering AUC. Simultaneous famotidine increased		When omeprazole 40 mg once daily was coadministered with the 3D regimen in healthy volunteers, omeprazole Cmax and AUC decreased 38% and paritaprevir Cmax increased 19%, AUC increased 18%, dasabuvir Cmax increased 13% and AUC increased 8%, and ombitasvir Cmax increased 2% and AUC increased 5%.[34] Monitor

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
BID or 300 mg qhs *Ranitidine 150 mg BID or 300 mg qhs* *<u>H2RAs (maintenance qhs dosing)</u>:* *Famotidine 20 mg* *Nizatidine 150 mg* *Ranitidine 150 mg*	daclatasvir is not required.[2] With coadministration of **omeprazole 40 mg daily** and single dose daclatasvir 60 mg, daclatasvir AUC decreased 16%, Cmax decreased 34% and Cmin decreased 8%. These changes are not considered clinically significant and dose adjustment of daclatasvir is not required.[2]	sofosbuvir Cmax by 15% without altering AUC, while staggered administration did not alter sofosbuvir or GS0331007 exposures. A separate group received **omeprazole 20 mg** daily alone or with single-dose ledipasvir/sofosbuvir. With omeprazole coadministration, ledipasvir AUC and Cmax were decreased 4% and 11% respectively, while sofosbuvir and GS-331007 exposures were not affected.[1] Ledipasvir/sofosbuvir may be given simultaneously with or 12 hours apart from H2RA at a dose not exceeding famotidine 40 mg BID. Ledipasvir/sofosbuvir may be given simultaneously with omeprazole 20 mg. It is recommended to separate ledipasvir/ sofosbuvir and antacids by 4 hours.[14]		patients for decreased efficacy of omeprazole. Consider increasing the omeprazole dose in patients whose symptoms are not well controlled; avoid use of more than 40 mg per day of omeprazole.[7]
Alprazolam	Dose adjustment of alprazolam, other benzodiazepines or other CYP3A4 substrates is not required when			When alprazolam 0.5 mg once daily was coadministered with the 3D regimen in healthy volunteers, alprazolam Cmax

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	coadministering with daclatasvir.[2]			increased 9% and AUC increased 167%. Pharmacokinetics of the 3D regimen were unchanged in the presence of alprazolam. Monitor for symptoms of increased alprazolam exposure and modify dose if required.[7, 34]
Amiodarone	Serious risk of symptomatic bradycardia if amiodarone is co-administered with sofosbuvir/ledipasvir or sofosbuvir plus another DAA. In post-marketing reports, bradycardia was observed within hours to days of starting a **SOF-DAA (ledipasvir, daclatasvir or simeprevir)** regimen in patients also on amiodarone. Symptomatic bradycardia, one fatal cardiac arrest, and cases requiring pacemaker insertion have been observed. Risk factors include co-administration of a beta-blocker, underlying cardiac comorbidities, or advanced liver disease. The mechanism of this potential interaction is unknown. **Avoid coadministration**	Serious risk of symptomatic bradycardia if amiodarone is co-administered with **sofosbuvir/ledipasvir** or sofosbuvir plus another DAA. In post-marketing reports, bradycardia was observed within hours to days of starting a SOF-DAA (ledipasvir, daclatasvir or simeprevir) regimen in patients also on amiodarone. Symptomatic bradycardia, one fatal cardiac arrest, and cases requiring pacemaker insertion have been observed. Risk factors include co-administration of a beta-blocker, underlying cardiac comorbidities, or advanced liver disease. The mechanism of this potential interaction is unknown. **Avoid coadministration of amiodarone with sofosbuvir-**		

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	of amiodarone with sofosbuvir-containing DAA regimens. If amiodarone therapy is needed, in-patient cardiac monitoring for the first 48 hours of coadministration is recommended, followed by daily outpatient or self-monitoring of heart rate for at least the first 2 weeks of treatment.(Dear Health Care Provider letter, Gilead Sciences, March 2015)	**containing DAA regimens.** If amiodarone therapy is needed, in-patient cardiac monitoring for the first 48 hours of coadministration is recommended, followed by daily outpatient or self-monitoring of heart rate for at least the first 2 weeks of treatment.(Dear Health Care Provider letter, Gilead Sciences, March 2015)		
Buprenorphine/ naloxone	When opioid-dependent adults on stable buprenorphine/ naloxone maintenance therapy received daclatasvir 60 mg once daily, buprenorphine AUC increased 37%, Cmax increased 40%, Cmin increased 20% and norbuprenorphine AUC increased 62%, Cmax increased 65% and Cmin increased 46%; daclatasvir exposures were not altered compared to historical data.[35] Combination may be given without dose adjustment.[2]			In 38 subjects on stable opioid replacement therapy (n=19 methadone, n=19 buprenorphine), administration of paritaprevir/ritonavir/ ombitasvir (150/100/25 mg QD) plus dasabuvir 250 mg BID and ribavirin for 12 weeks, no clinically evident treatment-emergent drug-drug interactions were noted, and treatment was well tolerated.[36] In the presence of the 3D regimen, buprenorphine Cmax was increased 118% and AUC was increased 107% and naloxone AUC was increased 18% and AUC was increased 28%. No dose adjustment of buprenorphine/nalox

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
				one is required.[34] Monitor patient for sedation and cognitive effects.[7]
Calcium channel blockers: amlodipine diltiazem nifedipine verapamil	Potential for increased daclatasvir concentrations. Use combination with caution.[2]			When amlodipine 5 mg once daily was coadministered with the 3D regimen in healthy volunteers, amlodipine Cmax increased 26% and AUC increased 34%. Paritaprevir Cmax decreased 23%, AUC decreased 22% and dasabuvir and ombitasvir pharmacokinetics were unchanged in the presence of amlodipine. The dose of amlodipine and other calcium channel blockers should be decreased by 50% when coadministering with the 3D regimen.[34]
Carbamazepine	Daclatasvir is contraindicated with strong inducers of CYP3A4 and/or P-glycoprotein.[2]	Potential for decreased concentrations of ledipasvir/sofosbuvir. Coadministration is not recommended.[14]		When carbamazepine 200 mg once daily for 3 days then 200 mg twice daily was coadministered with the 3D regimen in healthy volunteers, carbamazepine Cmax and AUC increased 10% and 17%, respectively, while paritaprevir Cmax decreased 66%, AUC decreased 70%, dasabuvir Cmax decreased 55%, AUC decreased 70%, and ombitasvir Cmax decreased 31% and AUC decreased 30%.

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
				Carbamazepine is contraindicated.[7, 34]
Clarithromycin	Potential for increased daclatasvir exposures due to CYP3A4 inhibition by clarithromycin. Reduce daclatasvir to 30 mg once daily with clarithromycin, telithromycin or other strong CYP3A4 inhibitors. Azithromycin may be used without dose adjustment.[2]			
Cyclosporine	Healthy subjects received single doses of cyclosporine 400 mg or tacrolimus 5 mg alone or in the presence of steady-state daclatasvir 60 mg daily. Daclatasvir did not affect the kinetics of either cyclosporine or tacrolimus, and daclatasvir exposures were not altered in the presence of tacrolimus. When coadministered with cyclosporine, modest increases in daclatasvir exposures (40% ↑ AUC, 56% ↑ C24) were observed. These changes are not considered clinically relevant. Dose adjustments are not required when daclatasvir is	No clinically significant drug interactions have been observed either with cyclosporine or tacrolimus.[14]		The impact of cyclosporine on the pharmacokinetics of AbbVie's 3D regimen (paritaprevir /ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) regimen was assessed in healthy volunteers. In the presence of cyclosporine, paritaprevir exposures were modestly increased (AUC increased 72%, Cmax increased 44%, C24 increased 85%) and dasabuvir exposures were modestly decreased (AUC decreased 30%, Cmax decreased 34%, C24 decreased 24%). No dose adjustment for the DAAs is recommended when dosed with cyclosporine.[33] When initiating

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	coadministered with cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil.[2, 37]			therapy with Viekira Pak, reduce cyclosporine dose to 1/5th of the patient's current cyclosporine dose. Measure cyclosporine blood concentrations to determine subsequent dose modifications. Upon completion of Viekira Pak therapy, the appropriate time to resume baseline doses of cyclosporine should be guided by assessment of cyclosporine blood concentrations. Frequent assessment of renal function and cyclosporine-related side effects is recommended.[7] A phase 1 study demonstrated a 3-fold increase in cyclosporine half-life and 7-fold increase in tacrolimus half-life when administered concomitantly with the AbbVie 3D regimen. Therefore, for the open-label phase II study (M12-999, CORAL-I) of the 3D regimen plus ribavirin in liver transplant recipients with recurrent HCV genotype 1 infection on stable cyclosporine or tacrolimus therapy, cyclosporine was reduced to 20% of

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
				the usual daily dose given once daily, while tacrolimus was reduced to either 0.5 mg once weekly or 0.2 mg every 3 days. Cyclosporine concentrations were maintained within the desired range with the recommended dosing modification (n=5). The tacrolimus dose was 0.5-1 mg at 1-2 week intervals for most patients, and tacrolimus trough levels were comparable pre-treatment and on-treatment (n=29).[38]
Dabigatran	Potential for increased dabigatran exposures due to P-gp inhibition by daclatasvir. Monitor closely for safety and efficacy.[2]			
Dexamethasone	Daclatasvir is contraindicated with strong inducers of CYP3A4.[2]			
Digoxin	With coadministration of digoxin 0.125 mg daily and daclatasvir 60 mg daily, digoxin AUC increased 27%, Cmax increased 65% and Cmin increased 18% due to P-gp inhibition by daclatasvir. Use combination with caution; initiate digoxin at lowest dose, monitor digoxin serum	Potential for increased concentrations of digoxin with coadministration. Monitoring of digoxin concentrations is recommended when coadministering with ledipasvir/sofosbuvir.[14]		The pharmacokinetics of the P-gp substrate digoxin 0.5 mg once daily alone or with AbbVie's 3D regimen (paritaprevir/ritonavir/ ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) regimen was assessed in healthy volunteers. Pharmacokinetics of the 3D regimen were unchanged in the presence of digoxin.

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	concentrations and titrate to desired clinical effect.[2] The combined effect of daclatasvir 60 mg daily plus asunaprevir 100 mg 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.[39]			The DAAs showed a minimal impact on the pharmacokinetics of digoxin (AUC increased 16%, Cmax increased 15%, Ctrough increased 1%).[33] A priori dose adjustments of digoxin are not required when coadministering with the Viekira Pak; monitoring of digoxin concentrations is recommended.[7, 34]
Duloxetine				When duloxetine 60 mg once daily was coadministered with the 3D regimen in healthy volunteers, duloxetine Cmax decreased 21% and AUC decreased 24%. Pharmacokinetics of the 3D regimen were

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
				unchanged in the presence of duloxetine. Dose adjustment of duloxetine or the 3D regimen are not required with coadministration.[7, 34]
Ergot derivatives: ergotamine dihydroergotamine ergonovine methylergonovin				Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Ergot derivatives are contraindicated**.[7, 34]
Escitalopram	Coadministration of escitalopram 10 mg daily and daclatasvir 60 mg once daily led to 12% increase AUC, 14% increase Cmax and 23% increase Cmin of daclatasvir, and 5% increase AUC and 10% increase Cmin of escitalopram. Combination may be given without dose adjustment.[2]			When escitalopram 10 mg once daily coadministered with the 3D regimen in healthy volunteers, escitalopram Cmax was unchanged and AUC decreased 13%. The pharmacokinetics of the 3D regimen were not significantly changed in the presence of escitalopram. Dose adjustment of escitalopram or the 3D regimen are not required with coadministration.[7, 34]
Fluconazole	Modest increases in daclatasvir exposures are expected but dose adjustment of daclatasvir is not required.[2]			
Fluticasone				Potential for increased fluticasone concentrations with inhaled or nasal fluticasone which may reduce serum cortisol

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
				concentrations. Alternative corticosteroids should be considered, particularly for long term use.[7]
Furosemide				When furosemide 20 mg once daily was coadministered with the 3D regimen in healthy volunteers, furosemide Cmax increased 42% and AUC increased 8%. Pharmacokinetics of the 3D regimen were unchanged in the presence of furosemide.[34] Clinical monitoring of patients is recommended and therapy should be individualized based on the patient's response.[7]
Gemfibrozil				The impact of gemfibrozil 600 mg BID on the pharmacokinetics of AbbVie's 3D regimen (paritaprevir/ritonavir/ ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) regimen was assessed in healthy volunteers. In the presence of gemfibrozil, dasabuvir Cmax increased 2-fold and AUC increased 11.3-fold and paritaprevir Cmax increased 21% and AUC increased 38%. **Gemfibrozil is contraindicated**.[7, 34]
HmgCoA reductase	With	Potential for		The

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
inhibitors (statins): atorvastatin lovastatin pravastatin rosuvastatin simvastatin	coadministration of rosuvastatin 10 mg single dose and daclatasvir 60 mg once daily, rosuvastatin AUC increased 58% and Cmax increased 104% due to inhibition of OATP1B1 and BCRP by daclatasvir. Exposures of other statins also expected to increase due to inhibition of OATP1B1 and/or BCRP by daclatasvir. Use combination with caution.[2]	significant increase in rosuvastatin concentrations; coadministration is not recommended.[14]		pharmacokinetics of pravastatin 10 mg or rosuvastatin 5 mg daily alone or with AbbVie's 3D regimen (paritaprevir /ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) regimen was assessed in healthy volunteers. With coadministration, pravastatin Cmax was increased 37%, AUC was increased 82% and the pharmacokinetics of the 3D regimen were unchanged. The pravastatin dose should be reduced by 50% (maximum dose of 40 mg daily) with the 3D regimen.[7, 33] When rosuvastatin was coadministered with the 3D regimen, rosuvastatin Cmax increased 7-fold and AUC increased 2.6-fold, while paritaprevir Cmax increased 59% and AUC increased 52% and dasabuvir and ombitasvir pharmacokinetics were unchanged. A maximum dose of 10 mg rosuvastatin should be used with the 3D regimen.[7, 33] **Lovastatin and simvastatin are contraindicated with the 3D**

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
				regimen.[7, 34]
Ketoconazole	Coadministration of ketoconazole 400 mg once daily and daclatasvir 10 mg single dose led to 200% increase AUC and 57% increase Cmax of daclatasvir. Reduce daclatasvir dose to 30 mg once daily when coadministered with ketoconazole, itraconazole, posaconazole, voriconazole or other strong inhibitors of CYP3A4.[2]		In healthy male subjects, the effect of multi-dose ketoconazole 400 mg QD on the pharmacokinetics of 50 mg single dose MK-8742 was evaluated. MK-8742 AUC ↑ 31%, Cmax ↓ 22% and C24h ↑ 38% in the presence of ketoconazole.[40]	The impact of ketoconazole 400 mg daily on the pharmacokinetics of AbbVie's 3D regimen (paritaprevir /ritonavir/ombitasvir 150/100/25 mg QD and dasabuvir 400 mg BID) regimen was assessed in healthy volunteers. In the presence of ketoconazole, paritaprevir exposures were increased (AUC increased 2-fold, Cmax increased 37%), ritonavir AUC increased 57% and Cmax increased 27%, and dasabuvir AUC increased 42%, Cmax increased 15%[33] Ketoconazole Cmax increased 16% and AUC increased 117% in the presence of 3D regimen. No dose adjustment for the DAAs is recommended when dosed with ketoconazole; a maximum dose of ketoconazole 200 mg should be used with the 3D regimen.[7, 34]
Methadone	When opioid-dependent adults on stable methadone maintenance therapy received daclatasvir 60 mg once daily, R-methadone AUC and Cmin increased		In 10 adult subjects on stable methadone maintenance therapy, administration of MK-8742 50 mg once daily for 10 days did not affect AUC of R or S-methadone, and no symptoms of opiate toxicity or	In 38 subjects on stable opioid replacement therapy (n=19 methadone, n=19 buprenorphine), administration of paritaprevir /ritonavir/ombitasvir 150/100/25 mg QD plus dasabuvir 250

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	8%, and Cmax increased 7%, while daclatasvir exposures were not altered compared to historical data.[35] Combination may be given without dose adjustment.[2]		withdrawal were observed. Exposures of MK-8742 in the presence of methadone were increased compared to historical controls (MK-8742 AUC increased 71%, Cmax increased 92%), but these changes are not considered clinically meaningful. MK-8742 may be coadministered with methadone without dose adjustment.[41]	mg BID and ribavirin for 12 weeks, no clinically evident treatment-emergent drug-drug interactions were noted, and treatment was well tolerated.[36] No dose adjustment of methadone is required when coadministering with the 3D regimen.[7, 34]
Midazolam	In healthy volunteers, steady-state administration of daclatasvir 60 mg once daily had minimal effect on the pharmacokinetics of single-dose midazolam 5 mg (AUC ↓ 13%, with GMR within the standard range for bioequivalence).[42] Dose adjustment of midazolam, other benzodiazepines or other CYP3A4 substrates is not required when coadministering with daclatasvir.[2]			Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Oral midazolam is contraindicated**.[7, 34]
Oral contraceptives	In 20 HCV-uninfected on hormonal contraception with Ortho Tri-Cyclen® (35 ug ethinyl estradiol/180-215-250 ug norgestimate), administration of daclatasvir 60 mg	In HCV-uninfected women on hormonal contraception with norgestimate/ethinyl estradiol (NGM/EE, Ortho Tri-Cyclen Lo®), administration of ledipasvir for 14 days resulted in 40% ↑ Cmax and 20% ↑	In 20 HCV-uninfected women, administration of MK-8742 50 mg once daily for 13 days did not significantly affect the pharmacokinetics of single-dose Nordette-28 (0.03 mg ethinyl estradiol/0.15 mg levonorgestrel).[46]	When coadministered with the 3D regimen in healthy volunteers, norethindrone Cmax and AUC decreased 17% and 9%, respectively. Progestin-only contraceptives may be used with the

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	daily for 10 days did not result in any clinically significant effects on the pharmacokinetics of ethinyl estradiol, norelgestromin or norgestrel. No loss in contraceptive efficacy is expected with coadministration of combined oral contraceptives and daclatasvir.[43] **<u>Daclatasvir-TRIO regimen (fixed-dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg):</u>** In healthy women subjects, coadministration of daclatasvir-TRIO with low-dose norethindrone (NE) 1000 ug/ethinyl estradiol (EE) 20 ug resulted in ~21% increase in NE Cmax and comparable AUC, and 16% decrease in EE AUC with comparable Cmax. In cycle 2 of the study, women received high-dose NE 1500 ug/EE 30 ug with daclatasvir-TRIO, and resulting NE and EE exposures (Cmax and AUC) were within the clinical equivalence boundaries when	AUC of EE, while NGM kinetics were unaffected. Ledipasvir kinetics were similar to historical data. FSH, LH and progesterone values were similar in all cycles. No loss in contraceptive efficacy is expected with coadministration of combined oral contraceptives containing ethinyl estradiol and norgestimate with ledipasvir.[45]		Viekira Pak.[7] Ethinyl estradiol-containing oral contraceptives are **contraindicated** with the Viekira Pak® due to the potential to increase ALT.[34] Discontinue ethinyl estradiol-containing medications prior to starting Viekira Pak® (alternative contraceptive methods are recommended). Perform hepatic laboratory testing on all patients during the first 4 weeks of treatment.

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	compared to exposure with low-dose NE/EE alone. Coadministration of high-dose NE acetate/EE with daclatasvir-TRIO is anticipated to be well tolerated and to provide effective contraception.[44]			
Phenobarbital	Daclatasvir is contraindicated with strong inducers of CYP3A4 and/or P-glycoprotein.[2]	Potential for decreased concentrations of ledipasvir/sofosbuvir. Coadministration is not recommended.[14]		Exposures of the 3D regimen may be significantly decreased by CYP3A inducers. **Phenobarbital is contraindicated**.[7, 34]
Phenytoin	Daclatasvir is contraindicated with strong inducers of CYP3A4 and/or P-glycoprotein.[2]	Potential for decreased concentrations of ledipasvir/sofosbuvir. Coadministration is not recommended.[14]		Exposures of the 3D regimen may be significantly decreased by CYP3A inducers. **Phenytoin is contraindicated**.[7, 34]
Pimozide				Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Pimozide is contraindicated**.[7, 34]
Rifabutin	Reduced daclatasvir exposures are expected with rifabutin due to CYP3A4 induction. Daclatasvir is contraindicated with rifabutin, rifapentine or other strong inducers of CYP3A4.[2]	Potential for decreased concentrations of ledipasvir/sofosbuvir, leading to reduced therapeutic effect. Coadministration is not recommended.[14]		
Rifampin	With coadministration of rifampin 600 mg daily and daclatasvir 60 mg	Potential for decreased concentrations of ledipasvir/sofosbuvir. Coadministration is		Exposures of the 3D regimen may be significantly decreased by CYP3A inducers. **Rifampin**

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	single dose, daclatasvir AUC decreased 79% and Cmax decreased 56%. Daclatasvir is contraindicated with strong inducers of CYP3A4 and/or P-glycoprotein.[2]	not recommended.[14]		**is contraindicated**.[7, 34]
Salmeterol				Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Salmeterol is not recommended**.[34] The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.[7]
Sildenafil	Dose adjustment of PDE5 inhibitors or other CYP3A4 substrates is not required when coadministering with daclatasvir.[2]			Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Sildenafil is contraindicated with the 3D regimen when used for the treatment of pulmonary arterial hypertension**.[7, 34]
St. John's Wort	Daclatasvir is contraindicated with strong inducers of CYP3A4 and/or P-glycoprotein.[2]	Potential for decreased concentrations of ledipasvir and sofosbuvir. Coadministration is not recommended.[14]		Exposures of the 3D regimen may be significantly decreased by CYP3A inducers. **St. John's wort is contraindicated**.[7, 34]
Tacrolimus	Healthy subjects received single doses of	No clinically significant drug interactions have		A phase 1 study demonstrated a 3-fold increase in

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
	cyclosporine 400 mg or tacrolimus 5 mg alone or in the presence of steady-state daclatasvir 60 mg daily. Daclatasvir did not affect the kinetics of either cyclosporine or tacrolimus, and daclatasvir exposures were not altered in the presence of tacrolimus. When coadministered with cyclosporine, modest increases in daclatasvir exposures (40% ↑ AUC, 56% ↑ C24) were observed. These changes are not considered clinically relevant. Dose adjustments are not required when daclatasvir is coadministered with cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil.[2, 37]	been observed either with cyclosporine or tacrolimus.[14]		cyclosporine half-life and 7-fold increase in tacrolimus half-life when administered concomitantly with the AbbVie 3D regimen. Therefore, for the open-label phase II study (M12-999, CORAL-I) of the 3D regimen plus ribavirin in liver transplant recipients with recurrent HCV genotype 1 infection on stable cyclosporine or tacrolimus therapy, cyclosporine was reduced to 20% of the usual daily dose given once daily, while tacrolimus was reduced to either 0.5 mg once weekly or 0.2 mg every 3 days. Cyclosporine concentrations were maintained within the desired range with the recommended dosing modification (n=5). The tacrolimus dose was 0.5-1 mg at 1-2 week intervals for most patients, and tacrolimus trough levels were comparable pre-treatment and on-treatment (n=29).[38] When initiating therapy with Viekira Pak, the dose of tacrolimus needs to be reduced. Do not administer tacrolimus on the day Viekira Pak is initiated.

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
				Beginning the day after Viekira Pak is initiated; reinitiate tacrolimus at a reduced dose based on tacrolimus blood concentrations. Typical tacrolimus dosing is 0.5 mg every 7 days. Measure tacrolimus blood concentrations and adjust dose or dosing frequency to determine subsequent dose modifications. Upon completion of Viekira Pak therapy, the appropriate time to resume pre-Viekira Pak dose of tacrolimus should be guided by assessment of tacrolimus blood concentrations. Frequent assessment of renal function and tacrolimus related side effects is recommended.[7]
Triazolam	Dose adjustment of triazolam, other benzodiazepines or other CYP3A4 substrates is not required when coadministering with daclatasvir.[2]			Exposures of sensitive CYP3A substrates may be significantly increased by the 3D regimen. **Triazolam is contraindicated**.[7, 34]
Voriconazole	Coadministration of ketoconazole 400 mg once daily and daclatasvir 10 mg single dose led to 200% increase AUC and 57% increase Cmax of daclatasvir.			Coadministration is not recommended due to potential for decreased voriconazole concentrations.[7]

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	**Ledipasvir (LDV, GS-5885) *Gilead***	**Elbasvir (MK-8742) *Merck***	**Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie***
	Reduce daclatasvir dose to 30 mg once daily when coadministered with ketoconazole, itraconazole, posaconazole, voriconazole or other strong inhibitors of CYP3A4.[2]			
Warfarin	Clinically significant interaction not expected. Combination may be administered without dose adjustment.[2]			When warfarin 5 mg once daily was coadministered with the 3D regimen in healthy volunteers, R-warfamin Cmax increased 6%, AUC decreased 12% and S-warfarin Cmax decreased 4% and AUC decreased 12%. Pharmacokinetics of the 3D regimen were unchanged in the presence of warfarin. No dose adjustment of warfarin is required when coadministering with the 3D regimen; monitor INR when initiating and discontinuing 3D regimen and adjust warfarin dosing if required.[7, 34]
Zolpidem	Dose adjustment of benzodiazepines or other CYP3A4 substrates is not required when coadministering with daclatasvir.[2]			When zolpidem 5 mg once daily was coadministered with the 3D regimen in healthy volunteers, zolpidem Cmax decreased 6% and AUC decreased 4%. Paritaprevir Cmax decreased 37% and AUC decreased 32%, ombitasvir and dasabuvir kinetics

	Daclatasvir (Daklinza®, DCV, BMS-790052) *Bristol-Myers Squibb*	Ledipasvir (LDV, GS-5885) *Gilead*	Elbasvir (MK-8742) *Merck*	Ombitasvir (Holkira Pak®/ Viekira Pak®, ABT-267) *Abbvie*
				were unchanged in the presence of zolpidem. Dose adjustment of zolpidem or the 3D regimen are not required with coadministration.[7, 34]

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. German P, Yang J, West S, et al. Effect of food and acid reducing agents on the relative bioavailability and pharmacokinetics of ledipasvir/sofosbuvir fixed dose combination tablet [abstract P_15]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, May 19-21, 2014, Washington, DC.

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

3. Kirby B, Mathias A, Yang C, et al. Metabolism and excretion of ledipasvir (GS-5885) in humans [abstract O_20]. 8th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 26-27, 2013, Cambridge, MA.

4. Mathias A. Clinical pharmacology of DAAs for hepatitis C: what's new and what's in the pipeline. 14th International Workshop on Clinical Pharmacology of HIV Therapy, April 22-24, 2013, Amsterdam.

5. Kirby B, Li H, Kearney BP, et al. Population pharmacokinetic analysis of ledipasvir (GS-5885) in healthy and hepatitis C virus infected subjects [abstract P_33]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, May 19-21, 2014, Washington, DC.

6. Marshall WL, Yeh W, Caro L, et al. Age and gender effects on the pharmacokinetics of HCV NS5A inhibitor MK-8742 [abstract PP_03]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, May 19-21, 2014, Washington, DC.

7. Abbvie Corporation. Viekira Pak (ombitasvir, paritaprevir and ritonavir tablets; dasabuvir tablets) Prescribing Information. North Chicago, IL December, 2014.

8. Bifano M, Sevinsky H, Persson A, et al. Single-dose pharmacokinetics of daclatasvir (DCV; BMS-790052) in subjects with hepatic impairment compared with healthy subjects [abstract]. 62nd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), November 6-9, 2011, San Francisco.

9. German P, Mathias A, Yang JC, et al. The pharmacokinetics of ledipasvir, an HCV specific NS5A inhibitor in HCV-uninfected subjects with moderate and severe hepatic impairment [abstract 467]. Hepatology 2013;58(4 (suppl)):432A.

10. Marshall WL, Garrett G, Yeh W, et al. Pharmacokinetics and safety of hepatitis C virus non-structural protein 5a inhibitor MK-8742 in cirrhotic patients with mild and moderate hepatic insufficiency [abstract P_41]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, May 19-21, 2014, Washington, DC.

11. Khatri A, Gaultier IA, Menon R, et al. Pharmacokinetics and safety of co-administered ABT-450 plus ritonavir (ABT 450/r), ABT-267 and ABT-333 as a single dose in subjects with normal hepatic function and in subjects with mild, moderate and severe hepatic impairment [abstract 758]. 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), November 9-13, 2012, Boston.

12. Garimella T, Wang R, Luo W-L, et al. The effect of renal impairment on single-dose pharmacokinetics to daclatasvir, an HCV NS5A inhibitor [abstract P_43]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, May 19-21, 2014, Washington, DC.

13. Mogalian E, Mathias A, Yang J, et al. The pharmacokinetics of ledipasvir, an HIV-specific NS5A inhibitor, in HCV-uninfected subjects with severe renal impairment [abstract]. . 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), November 7-11, 2014, Boston, MA.

14. Gilead Sciences Inc. Harvoni (ledipasvir/sofosbuvir) Product Monograph. Foster City, CA October, 2014.

15. 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.

16. 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.

17. Yeh W, Fraser IP, Bifano M, et al. Lack of pharmacokinetic interaction between HCV protease inhibitor MK-5172 and HCV NS5A inhibitor daclatasvir in healthy volunteers [abstract 464]. Hepatology 2013;58(4 (suppl)):430A.

18. Eley T, You X, Huang S, et al. Evaluation of drug interaction potential between daclatasvir and sofosbuvir [abstract O_14]. 8th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 26-27, 2013, Cambridge, MA.

19. German P, Mathias A, Pang PS, et al. Lack of a clinically significant pharmacokinetic drug-drug interaction between sofosbuvir (GS-7977) and GS-5885 or GS-9669 in healthy volunteers [abstract 1888]. 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), November 9-13, 2012, Boston.

20. Bifano M, Hwang C, Oosterhuis B, et al. Assessment of HIV ARV drug interactions with the HCV NS5A replication complex inhibitor BMS-790052 demonstrates a pharmacokinetic profile which supports co-administration with tenofovir disoproxil fumarate, efavirenz, and atazanavir/ritonavir [abstract 618]. 19th Conference on Retroviruses and Opportunistic Infections, March 5-8, 2012, Seattle, WA.

21. German P, Garrison K, Pang P, et al. Drug-drug interactions between anti-HCV regimen ledipasvir/sofosbuvir and antiretrovirals [abstract 82]. Conference on Retroviruses and Opportunistic Infections (CROI), February 23-26, 2015, Seattle, WA.

22. Gilead Sciences Canada Inc. Harvoni (ledipasvir/sofosbuvir) Product Monograph. Mississauga, ON October 14, 2014.

23. Yeh WY, Marshall W, Ma J, et al. Ritonavir-boosted atazanavir, lopinavir, & darunavir increase HCV NS5A inhibitor MK-8742 levels [abstract 635]. Conference on Retroviruses and Opportunistic Infections (CROI), March 3-6, 2014, Boston, MA.

24. Khatri A, Wang T, Wang H, et al. Drug-drug interactions of the direct acting antiviral regimen of ABT-450/r, ombitasvir and dasabuvir with HIV protease inhibitors [abstract V-484]. 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 5-9, 2014, Washington, DC.

25. Eley T, You X, Wang R, et al. Daclatasvir: Overview of drug–drug interactions with antiretroviral agents and other common concomitant drugs [abstract]. HIV DART, December 9-12, 2014, Miami, FL.

26. Song I, Jerva F, Zong J, et al. Evaluation of drug interactions between dolutegravir and daclatasvir in healthy subjects [abstract 79]. 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, May 26-28, 2015, Washington, DC.

27. Garrison K, Custodio J, Pang P, et al. Drug interactions between anti-HCV antivirals ledipasvir/sofosbuvir and integrase strand transfer inhibitor-based regimens [abstract 71]. 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, May 26-28, 2015, Washington, DC.

28. Yeh W, Feng HP, Guo Z, et al. Drug-drug interaction between HCV inhibitors grazoprevir/elbasvir with dolutegravir [abstract 522]. Conference on Retroviruses and Opportunistic Infections (CROI), February 23-26, 2015, Seattle, WA.

29. German P, Pang P, West S, et al. Drug interactions between direct acting anti-HCV antivirals sofosbuvir and ledipasvir and HIV antiretrovirals [abstract O_06]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, May 19-21, 2014, Washington, DC.

30. Yeh W, Marshall W, Mangin E, et al. Pharmacokinetic interactions between the HCV NS5A inhibitor MK-8742 and efavirenz [abstract 498]. Conference on Retroviruses and Opportunistic Infections (CROI), March 3-6, 2014, Boston, MA.

31. Khatri A, Wang T, Wang H, et al. Drug-drug interactions of the direct acting antiviral regimen of ABT-450/r, ombitasvir and dasabuvir with emtricitabine + tenofovir, raltegravir, rilpivirine and efavirenz [abstract V-483]. 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 5-9, 2014, Washington, DC.

32. 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.

33. Menon R, Badri P, Khatri A, et al. ABT-450/ritonavir +ombitasvir + dasabuvir: drug interactions mediated by transporters. 15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, May 19-21, 2014, Washington, DC.

34. Menon R, Badri P, Das U, et al. Drug-drug interactions with direct acting antiviral combination therapy of ABT-450/r, ombitasvir and dasabuvir [abstract A-007]. 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 5-9, 2014, Washington, DC.

35. Garimella T, Wang R, Luo W-L, et al. Evaluation of drug-drug interaction between daclatasvir and methadone or buprenorphine/naloxone [abstract 1166]. IDWeek 2014™, October 8-12, 2014, Philadelphia, PA.

36. Lalezari J, Sullivan J, Rustgi V, et al. Abbvie IFN-free 3 DAA regimen in HCV genotype 1-infected patients on methadone or buprenorphine [abstract]. 21st Annual Conference on Retroviruses and Opportunistic Infections, March 3-6, 2014, Boston, MA.

37. Bifano M, Adamczyk R, Hwang C, et al. Daclatasvir pharmacokinetics in healthy subjects: no clinically-relevant drug-drug interactions with either cyclosporine or tacrolimus [abstract 1081]. Hepatology 2013;58(4 suppl):730A.

38. Kwo PJ, Mantry PS, Coakley E, et al. Results of the phase 2 study M12-999: interferon-free regimen of ABT-450/r/ABT-267 + ABT-333 + ribavirin in liver transplant recipients with recurrent HCV genotype 1 infection [abstract O114]. 49th Annual Meeting of the European Association for the Study of the Liver (EASL), April 9-13, 2014, London, England.

39. 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.

40. Yeh W, Marshall WL, Caro L, et al. Pharmacokinetic interaction of HCV NS5A inhibitor MK-8742 and ketoconazole in healthy subjects [P_27]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, May 19-21, 2014, Washington, DC.

41. Marshall W, Jumes P, Yeh W, et al. Lack of PK interaction between the hepatitis c virus non-structural protein 5a inhibitor MK-8742 and methadone in subjects on stable opiate maintenance therapy [abstract]. HEP DART, December 8-12, 2013, Hawaii.

42. Bifano M, Sevinsky H, Stonier M, et al. Daclatasvir, an HCV NS5A replication complex inhibitor, has minimal effect on pharmacokinetics of midazolam, a sensitive probe for cytochrome P450 3A4 [abstract O_15]. 8th International Workshop on Clinical Pharmacology of Hepatitis Therapy, June 26-27, 2013, Cambridge, MA.

43. Bifano M, Sevinsky H, Persson A, et al. Daclatasvir (DCV; BMS-790052) has no clinically significant effect on the pharmacokinetics of a combined oral contraceptive containing ethinyl estradiol and norgestimate in healthy female subjects [abstract]. 62th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), November 6-9, 2011, San Francisco, CA.

44. Adamczyk R, Lubin S, Hesney M, et al. Effect of daclatasvir with asunaprevir and beclabuvir on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norethindrone acetate in women [abstract 78]. 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, May 26-28, 2015, Washington, DC.

45. German P, Moorehead L, Pang PS, et al. Lack of a clinically important pharmacokinetic interaction between norgestimate/ethinyl estradiol and sofosbuvir (SOF) or ledipasvir (LDV) in HCV-uninfected female subjects [abstract 469]. Hepatology 2013;58(4 (suppl)):433A.

46. Marshall W, Yeh W, Caro L, et al. No pharmacokinetic interaction between the hepatitis c virus non-structural protein 5a inhibitor MK-8742 and ethinyl estradiol and levonorgestrel [abstract]. HEPDART, Dec 8-12, 2013, Hawaii.