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Drug Interactions with the Direct-Acting Antiviral Combination of Ombitasvir and Paritaprevir-Ritonavir

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The two direct-acting antiviral (2D) regimen of ombitasvir and paritaprevir (administered with low-dose ritonavir) is being developed for treatment of genotype subtype 1b and genotypes 2 and 4 chronic hepatitis C virus (HCV) infection. Drug-drug interactions were evaluated in healthy volunteers to develop dosing recommendations for HCV-infected subjects. Mechanism-based interactions were evaluated for ketoconazole, pravastatin, rosuvastatin, digoxin, warfarin, and omeprazole. Interactions were also evaluated for duloxetine, escitalopram, methadone, and buprenorphine-naloxone. Ratios of geometric means with 90% confidence intervals for the maximum plasma concentration and the area under the plasma concentration-time curve were estimated to assess the magnitude of the interactions. For most medications, coadministration with the 2D regimen resulted in a <50% change in exposures. Ketoconazole, digoxin, pravastatin, and rosuvastatin exposures increased by up to 105%, 58%, 76%, and 161%, respectively, and omeprazole exposures decreased by approximately 50%. Clinically meaningful changes in ombitasvir, paritaprevir, or ritonavir exposures were not observed. In summary, all 11 medications evaluated can be coadministered with the 2D regimen, with most medications requiring no dose adjustment. Ketoconazole, digoxin, pravastatin, and rosuvastatin require lower doses, and omeprazole may require a higher dose. No dose adjustment is required for the 2D regimen.

The treatment outcomes for patients with chronic hepatitis C virus (HCV) infection have improved considerably in recent years due to the development of direct-acting antiviral agents (DAAs) that target various steps in the HCV life cycle (1, 2). These agents produce higher response rates and have fewer toxicities than the previous interferon-based therapies.

Ombitasvir, a potent NS5A inhibitor, and paritaprevir, a potent NS3/4A protease inhibitor identified for clinical development by AbbVie and Enanta, both show *in vitro* antiviral activity against HCV subtypes 1a, 1b, 2a, 3a, 4a, and 6a (3–5). Paritaprevir is administered with low-dose (100 mg) ritonavir to increase the paritaprevir peak and trough concentrations and the overall drug exposure (6). The all-oral, interferon-free two-DAA (2D) regimen of ombitasvir and paritaprevir-ritonavir with or without ribavirin has been evaluated in clinical studies in patients with HCV genotype 1b, 2, 3, and 4 infection (7–9). The 2D regimen has been approved in the European Union (EU) for the treatment of patients with chronic HCV genotype 4 infection, including those with compensated cirrhosis. The three-DAA (3D) regimen of ombitasvir, paritaprevir-ritonavir, and dasabuvir has been approved with ribavirin for the treatment of chronic HCV genotype 1a infection and without ribavirin for the treatment of chronic HCV 1b infection in the United States and the EU (10–12). In addition, the 2D regimen is being developed in Japan for the treatment of HCV subtype 1b and genotype 2 infection (8). Dasabuvir is not active against genotypes other than genotype 1 (10, 12); therefore, it is not part of the 2D regimen, which is intended to be used for other genotypes.

The *in vitro* metabolic profile of the 2D regimen (13) indicates that paritaprevir and ritonavir are primarily metabolized by cytochrome P450 3A (CYP3A), and ombitasvir is predominantly metabolized by amide hydrolysis followed by oxidative metabolism. Ritonavir is a CYP3A inhibitor, whereas the DAAs do not inhibit CYP enzymes. *In vitro* data also suggest that at clinically relevant concentrations, paritaprevir is an organic anion-transporting polypeptide 1B1/B3 (OATP1B1/B3) inhibitor, and paritaprevir and ritonavir are potential inhibitors of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). The DAAs and ritonavir are *in vitro* substrates of P-gp. Paritaprevir is also a substrate of BCRP and OATP1B1/B3.

A broad drug-drug interaction program was conducted in healthy volunteers to evaluate the potential for drug interactions with this 2D regimen. These studies characterized the mechanism-based (i.e., enzyme- or transporter-related) interactions using probe substrates and inhibitors based on regulatory guidances (14, 15) and the interactions that may occur with commonly used medications in HCV-infected patients (13, 16, 17). The results from these studies were used to develop dosing recommendations for patients treated with the 2D regimen.

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TABLE 1 Medications evaluated in the drug-drug interaction studies with the 2D regimen of ombitasvir and paritaprevir-ritonavir

	Mechanism-based drug-drug interactions			Drug interactions with commonly used medications	
Drug class	No. of subjects	Medication (dose)	Mechanism	No. of subjects	Medication (metabolic pathway) (dose)
Antifungals	12	Ketoconazole (400 mg once daily)	Effect of CYP3A and P-gp inhibition by ketoconazole on the 2D regimen		
Anticoagulants	12	Warfarin (5 mg)	Effect of CYP2C9 inhibition/induction by the 2D regimen on warfarin		
Acid-reducing agents	12	Omeprazole (40 mg once daily)	Effect of CYP2C19 inhibition/induction by the 2D regimen on omeprazole		
Antiarrhythmics	12	Digoxin (0.5 mg)	Effect of P-gp inhibition by the 2D regimen on digoxin		
Statins	12	Pravastatin (10 mg once daily)	Effect of OATP1B1/B3 inhibition by the 2D regimen on pravastatin		
	12	Rosuvastatin (5 mg once daily)	Effect of OATP1B1/B3 + BCRP inhibition by the 2D regimen on rosuvastatin		
Antiaddictives				12	Methadone (CYP3A4/CYP2B6 substrate) (individualized once-daily dosing 20−120 mg per physician's prescription)
				11	Buprenorphine (CYP3A4; UGT1A1[a] substrate) (individualized once-daily dosing 4−24 mg per physician's prescription)
					Naloxone (UGT substrate) (individualized once-daily dosing 1−6 mg per physician's prescription)
Antidepressants				12	Escitalopram (CYP3A4/CYP2C19 substrate) (10 mg)
				12	Duloxetine (CYP2D6/CYP1A2 substrate and CYP1A2 inhibitor) (60 mg)

[a] UGT1A1, UDP glucuronosyltransferase 1A1.

MATERIALS AND METHODS

Study designs. Eight open-label, phase 1 clinical studies were conducted in healthy volunteers in accordance with good clinical practice guidelines and ethical principles that have their origin in the Declaration of Helsinki. The studies were performed among 4 clinical study sites in the United States and Canada between July 2012 and September 2013. The study protocols and amendments were approved by the institutional review boards, and written informed consent was obtained from each subject before any study-related procedures were performed. These studies included multiple treatment arms, and the results from the arms that received the three-DAA (3D) regimen of ombitasvir, paritaprevir-ritonavir, and dasabuvir have been reported previously (18). The results from the treatment arms that received the 2D regimen are the primary focus of this report.

Inhibitors of metabolic enzymes and drug transporters were not allowed within 1 month of enrollment. The subjects enrolled in the methadone and buprenorphine-naloxone studies had been taking stable doses of methadone or buprenorphine-naloxone for a minimum of 14 days before the screening visit. Subjects with clinically significant renal disease were excluded from participation in all studies.

The drug-drug interactions were evaluated for the 2D regimen of ombitasvir (25 mg) and paritaprevir-ritonavir (150/100 mg) using 11 medications from several different drug classes (Table 1). The key aspects of the study designs are presented in Fig. 1. Most evaluations were conducted under once-daily, multiple-dosing conditions, although a few mechanism-based interactions were evaluated under single-dosing conditions. For all evaluations, ombitasvir and paritaprevir-ritonavir were coadministered with the interacting medications after consumption of a moderate-fat meal (approximately 1,900 to 2,300 cal/day with 40% of calories from fat).

Safety and tolerability. The safety and tolerability of the 2D regimen and the interacting medications were assessed based on adverse event monitoring, physical examinations, laboratory tests, vital signs, and electrocardiogram assessments.

Pharmacokinetic evaluations. Intensive pharmacokinetic sampling was performed as noted in Fig. 1 for determination of the plasma concentrations of paritaprevir, ritonavir, ombitasvir, and the interacting medications and their metabolites, if applicable. The plasma concentrations were determined using validated liquid chromatography with tandem mass spectrometric detection methods. The lower limits of quantitation (LLOQs) for paritaprevir, ritonavir, and ombitasvir were 0.6 ng/ml {interrun accuracy (percent bias), −1.0% to 4.5%; interrun precision (percent coefficient of variation [%CV]), 5.0% to 7.0%}, 4.9 ng/ml (percent bias, −4.3% to −0.1%; %CV, 2.8% to 4.2%), and 0.5 ng/ml (percent bias, 0.7% to 4.7%; %CV, 3.8% to 5.3%), respectively. The LLOQs for the concomitant medications were 0.01 ng/ml for digoxin (percent bias, −3.99% to 2.05%; %CV, 3.71% to 9.64%), 0.02 ng/ml for naloxone (percent bias, −2.8% to −0.9%; %CV, 1.9% to 3.5%), 0.05 ng/ml for *S*-desmethylcitalopram (percent bias, −5.01% to 3.24%; %CV, 2.97% to 11.71%), 0.1 ng/ml for buprenorphine (percent bias, −3.7% to 0.0%; %CV, 2.4% to 3.2%), norbuprenorphine (percent bias, −3.0% to −1.1%; %CV, 2.7% to 4.6%), and rosuvastatin (percent bias, −0.281% to 1.76%; %CV, 0.915% to 3.87%), 100 ng/ml for ketoconazole (percent bias, −2.75% to −0.796%; %CV, 1.83% to 3.54%), 0.2 ng/ml for escitalopram (percent bias, −3.94% to 3.12%; %CV, 3.36% to 5.53%), 0.5 ng/ml for duloxetine (percent bias, −4.19 to 3.87%; %CV, 2.81% to 6.06%) and pravastatin (percent bias, −1.63% to 1.53%; %CV, 3.99% to 7.80%), 1 ng/ml for *R*-methadone (percent bias, 0.4% to 3.3%; %CV, 1.6% to 3.1%), *S*-methadone (percent bias, 1.1% to 3.2%; %CV, 2.1% to 3.2%), and omeprazole (percent bias, −0.9% to 4.4%; %CV, 4.7% to 9.7%), and 5 ng/ml for *R*-warfarin (percent bias, −6.74% to 0.473%; %CV, 4.17% to 5.42%) and *S*-warfarin (percent bias, −6.78% to 1.38%; %CV, 3.83% to 5.90%). For digoxin, urine was also collected and the excreted fraction of the drug was measured (LLOQ of 2 ng/ml; percent bias, −7.80% to −0.63%; %CV, 4.99% to 18.22%).

Pharmacokinetic analyses were performed by noncompartmental methods using Phoenix WinNonlin, version 6.0 or above (Pharsight, St. Louis, MO). The main pharmacokinetic parameters of interest were the maximum observed plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) during a dosing interval (AUC_{24}) or from time zero to infinity (AUC_{∞} for a single dose). Additional pharmacokinetic parameters of interest included the time to C_{max} (T_{max}), the 24-h concentration (C_{24}), and the terminal phase elimination half-life ($t_{1/2}$).

Pharmacodynamic evaluations. Pharmacodynamic measurements were performed to monitor for signs of withdrawal that could have been

I

Period 1	Washout	Period 2		
Day 1		A	B	C
DAAs		Ketoconazole (Days 8-9)	DAAs + Ketoconazole (Day 10)	Ketoconazole (Days 11-13)

N = 12. Intensive PK sampling (9-10 samples within 24 hours) was performed on Day 1/Period 1, Day 9/Period 2A, and Day 10/Period 2B. Additional samples were collected as needed to characterize terminal phase elimination half-lives.

II

Period 1	Washout	Period 2		
Single Dose		A*	B*	C*
Interacting Medication		DAAs	DAAs + Interacting Medication	DAAs
		*Days of Dosing		
Warfarin study		Days 15-28	Day 29	Days 30-38
Omeprazole study		Days 6-19	Days 20-24	NA
Digoxin study		Days 11-24	Day 25	Days 26-29
Escitalopram study		Days 7-20	Day 21	Days 22-26
Duloxetine study		Days 7-20	Day 21	Day 22

N = 12 per study. Intensive PK sampling (10-12 samples within 24 hours) was performed on Day 1/Period 1 (all studies), the last day of dosing in Period A (all studies), the first and last day of dosing in Period 2B (omeprazole study), and the only day of dosing in Period 2B (all other studies). Additional samples were collected as needed to characterize terminal phase elimination half-lives.

III

Period 1	Washout	Period 2	
Single Dose		3 to 7 Days of Dosing †	14 Days of Dosing
DAAs		Pravastatin or Rosuvastatin	DAAs + Pravastatin or Rosuvastatin

† 3 days for pravastatin (Study Days 1-3); 7 days for rosuvastatin (Study Days 1-7)

N = 12 for each statin. Intensive PK sampling (10-11 samples within 24 hours) was performed on Day 1 in Period 1 and on the first and last day of dosing with the statins alone and the statins + DAAs in Period 2. Additional samples were collected as needed to characterize terminal phase elimination half-lives.

IV

Days 1-8	Days 9-22	Days 23-25
Methadone or Buprenorphine/ Naloxone	DAAs + Methadone or Buprenorphine/Naloxone	Methadone or Buprenorphine/ Naloxone

N = 12 for methadone and 11 for buprenorphine/naloxone. Intensive PK sampling (10-13 samples within 24 hours) was performed on Days 8, 9, and 22. Additional samples were collected as needed to characterize terminal phase elimination half-lives.

FIG 1 Study designs used for evaluating the 11 drug interactions. PK, pharmacokinetic.

caused by changes in methadone and buprenorphine-naloxone exposures during coadministration with the 2D regimen. The pupil diameter and two self-administered instruments (the short opiate withdrawal scale score and the desire for drugs questionnaire) were measured before and during coadministration.

Statistical analyses. Statistical analyses were conducted using SAS, version 9.2 (SAS Institute, Inc., Cary, NC). The effects of ombitasvir and paritaprevir-ritonavir on the interacting medications and vice versa were estimated by analysis of $\log_e$-transformed C_{max} and AUC values under a repeated-measures analysis framework. The geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for C_{max} and AUC were calculated to quantify the magnitude of drug interactions.

RESULTS

Subject demographics. A total of 119 subjects, 76% of whom were male, received at least one dose of the 2D regimen and/or interacting medication in these studies. The demographics of subjects across the studies were similar: the ages of the subjects ranged from 20 to 55 years, the mean age ranged from 30.3 to 39.1 years, and the median body weight ranged from 72.5 to 80.0 kg. Across the arms receiving the 2D regimen, 60.5% of the subjects were white, 34.5% were black, 2.5% were Asian, and 2.5% were other races.

Pharmacokinetics. (i) Mechanism-based drug-drug interactions. The results from the studies of the mechanism-based interactions of the substrates and inhibitors of CYPs and the substrates of drug transporters on ombitasvir, paritaprevir, and ritonavir exposures are shown in Fig. 2, and the effects of ombitasvir and paritaprevir-ritonavir on the substrates and inhibitors are shown in Fig. 3. The pharmacokinetic parameters for ombitasvir, paritaprevir, ritonavir, and the substrates and inhibitors are presented

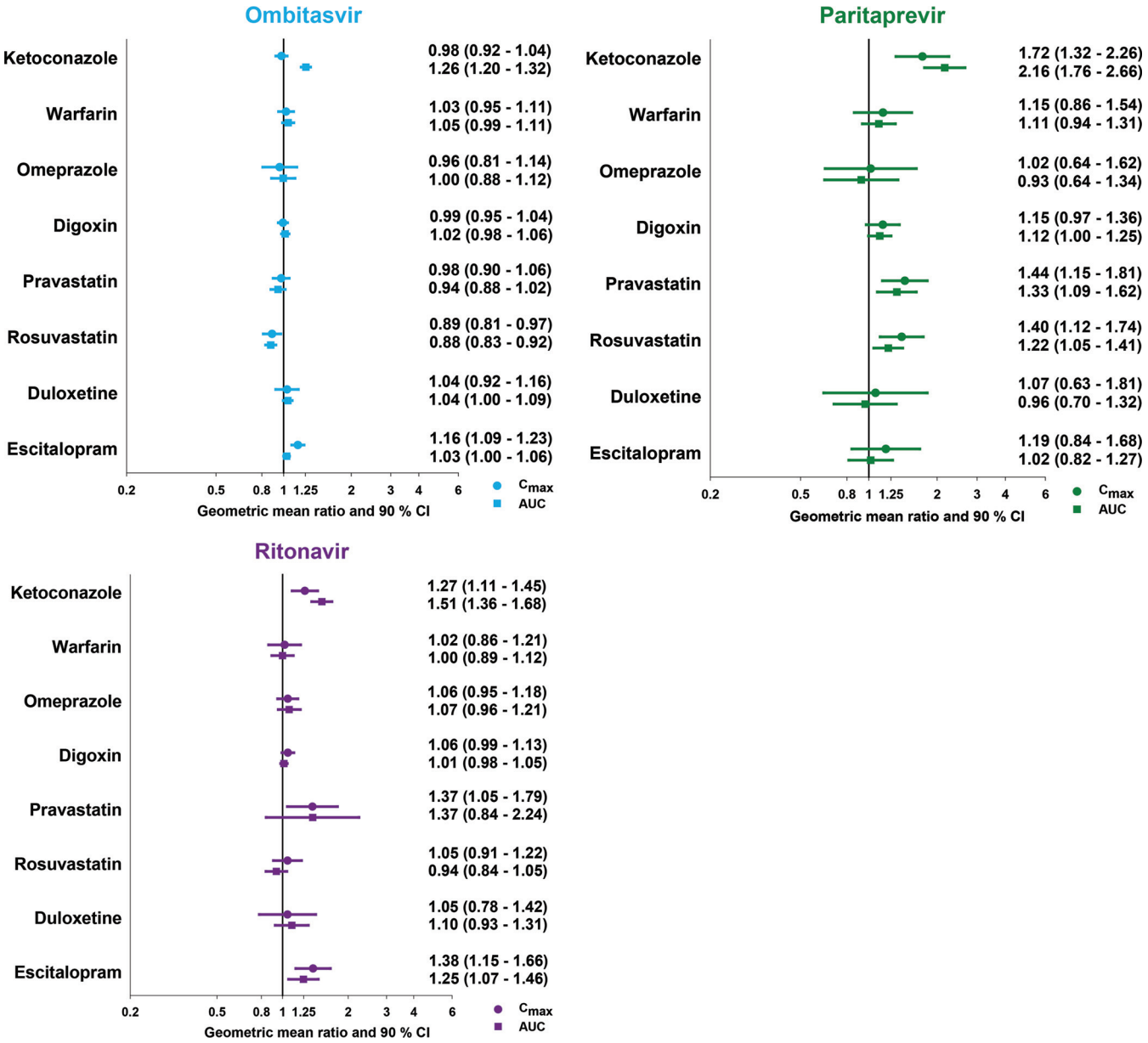

FIG 2 Effect of concomitant medications on the C_{max} and AUC values of ombitasvir, paritaprevir, and ritonavir. The geometric mean ratios indicate the C_{max} and AUC values for coadministration of the 2D regimen of ombitasvir and paritaprevir-ritonavir with the medication versus administration of the 2D regimen alone.

in Table 2. The magnitude of each drug interaction is discussed below.

(a) CYP3A and P-gp inhibitor (ketoconazole). When ketoconazole was coadministered with the 2D regimen, the ketoconazole C_{max} was not affected (10% increase), but the ketoconazole AUC increased by 105%. The mean $t_{1/2}$ of ketoconazole was almost 4-fold longer (16.0 versus 4.3 h) in the presence of ombitasvir and paritaprevir-ritonavir. Increased C_{max} and AUC values were also observed for paritaprevir (72% and 116%, respectively) and ritonavir (27% and 51%, respectively). The ombitasvir C_{max} was not affected (2% decrease), but the AUC increased by 26%. The mean $t_{1/2}$ of paritaprevir was more than 2-fold longer (14.4 versus 6.2 h), and the mean $t_{1/2}$ of ombitasvir increased from 24.9 to 39.5 h.

(b) CYP2C9 substrate (warfarin). Coadministration of warfarin with the 2D regimen did not affect *R*- or *S*-warfarin exposures (≤15% change in the C_{max} and AUC values) or ombitasvir, paritaprevir, or ritonavir exposures (≤15% change in the C_{max} and AUC values).

(c) CYP2C19 substrate (omeprazole). In the presence of the 2D regimen, the C_{max} and AUC values of omeprazole were reduced by 52% and 54%, respectively. Paritaprevir, ritonavir, and ombitasvir exposures were relatively unchanged (≤7% change in the C_{max} and AUC values) by coadministration with omeprazole.

(d) P-gp substrate (digoxin). When digoxin was coadministered with the 2D regimen, the values for digoxin C_{max}, AUC, and C_{24} increased by 58%, 36%, and 24%, respectively. There was no change in the fraction of unchanged drug eliminated in the urine

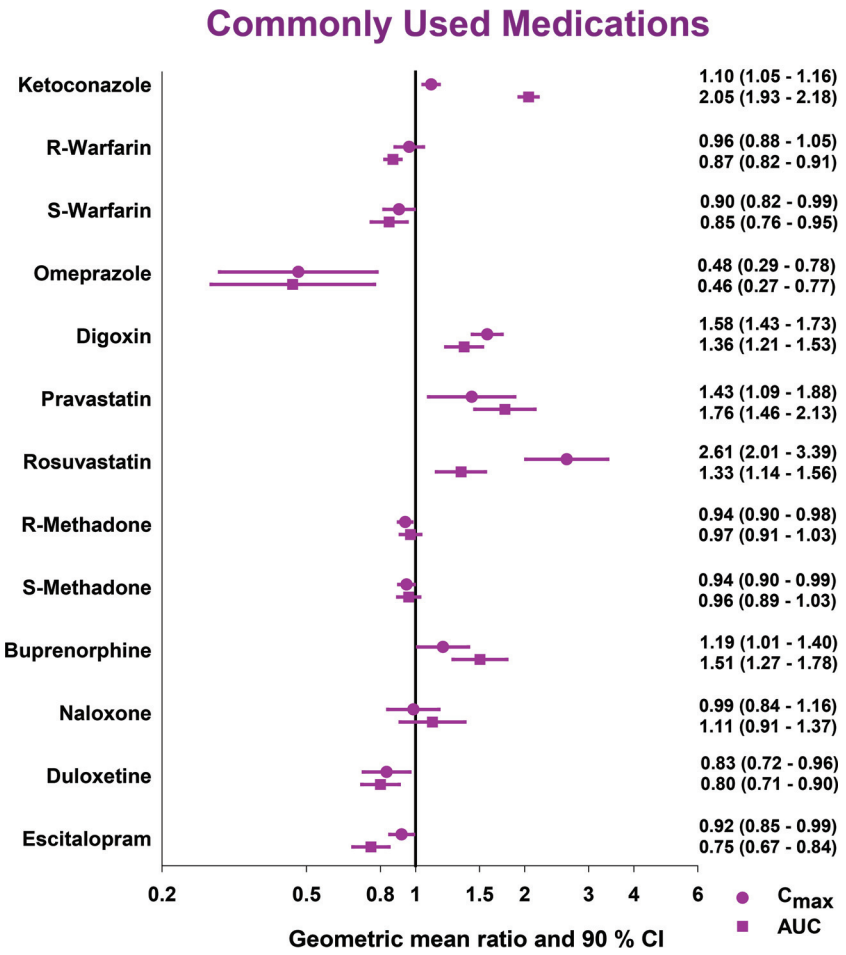

FIG 3 Effect of the 2D regimen of ombitasvir and paritaprevir-ritonavir on the C_{max} and AUC values of the concomitant medications. The geometric mean ratios indicate the C_{max} and AUC values for coadministration of the medication with the 2D regimen versus administration of the medication alone.

(ratio of fraction excreted, 1.01). Ombitasvir, paritaprevir, and ritonavir exposures were not affected by coadministration with digoxin (≤15% change in the C_{max} and AUC values).

(e) OATP1B1/B3 substrate (pravastatin). Coadministration of pravastatin with the 2D regimen increased the pravastatin C_{max} and AUC values by 43% and 76%, respectively. Coadministration increased the paritaprevir C_{max} and AUC values by 44% and 33% and increased the ritonavir C_{max} and AUC values by 37% each, but had no effect on the ombitasvir C_{max} or AUC value (≤6% decrease).

(f) OATP1B1/B3 and BCRP substrate (rosuvastatin). Rosuvastatin exposures increased in the presence of the 2D regimen: C_{max} increased by 161% and AUC increased by 33%. The paritaprevir C_{max} and AUC values increased by 40% and 22%, respectively, but the ritonavir and ombitasvir exposures were minimally affected (≤12% change in C_{max} and AUC values).

(ii) Interactions with commonly used medications. The effects of the 2D regimen on exposures of medications commonly used in HCV-infected patients are presented in Fig. 3, and the effects of these commonly used medications on the exposures of ombitasvir, paritaprevir, and ritonavir are presented in Fig. 2. The pharmacokinetic parameters for the DAAs, ritonavir, and the commonly used medications are presented in Table 2.

(a) Addiction treatment medications (methadone and buprenorphine-naloxone). Coadministration of the 2D regimen with methadone did not affect the *R*- or *S*-methadone exposure (≤6% decrease in the C_{max} and AUC values). Likewise, coadministration did not affect naloxone exposures (≤11% change in the C_{max} and AUC values). In contrast, the buprenorphine C_{max} and AUC values increased by 19% and 51%, respectively, and the norbuprenorphine C_{max} and AUC values increased by 82% and 111%, respectively, upon coadministration. The increases in the buprenorphine and norbuprenorphine exposures did not appear to have an effect on the pharmacodynamics of these medications, as there were no significant changes in the pupil diameter, the opioid withdrawal scale score, or the desire for drug questionnaire score upon coadministration with ombitasvir and paritaprevir-ritonavir.

(b) Antidepressants (escitalopram and duloxetine). In the presence of the 2D regimen, the C_{max} and AUC values of escitalopram, its metabolite *S*-desmethylcitalopram, and duloxetine were not affected (≤20% change) except for a 25% decrease in the escitalopram AUC. The exposures of ombitasvir, paritaprevir, and ritonavir were not affected by coadministration with duloxetine (≤10% change in the C_{max} and AUC values) but were increased by 2% to 38% by coadministration with escitalopram.

TABLE 2 Pharmacokinetic parameters for ombitasvir, paritaprevir, ritonavir, and coadministered medications in each study[a]

Study	C_{max} (ng/ml)		AUC (ng · h/ml)	
	Alone	Coadministration	Alone	Coadministration
Ketoconazole				
Paritaprevir	972 (70)	1,675 (62)	6,070 (61)[b]	13,100 (51)[b]
Ritonavir	1,460 (41)	1,850 (29)	9,440 (55)[b]	14,300 (38)[b]
Ombitasvir	113 (15)	110 (16)	1,700 (19)[b]	2,130 (17)[b]
Ketoconazole	11.1 (20)	12.2 (20)	86.5 (22)[c]	177 (21)[c]
Warfarin				
Paritaprevir	934 (113)	1,080 (106)	5,300 (113)[d]	5,870 (102)[d]
Ritonavir	2,030 (29)	2,070 (35)	11,700 (31)[d]	11,700 (31)[d]
Ombitasvir	124 (17)	127 (18)	1,210 (23)[d]	1,270 (20)[d]
R-Warfarin	269 (11)	255 (16)	19,900 (21)[b]	16,700 (19)[b]
S-Warfarin	272 (12)	240 (14)	13,000 (25)[b]	11,000 (33)[b]
Omeprazole				
Paritaprevir	2,020 (76)	2,060 (97)	11,100 (85)[d]	10,300 (101)[d]
Ritonavir	2,140 (25)	2,260 (29)	13,700 (29)[d]	14,600 (34)[d]
Ombitasvir	138 (36)	132 (36)	1,490 (39)[d]	1,480 (38)[d]
Omeprazole	334 (107)	159 (164)	1,170 (128)[c]	535 (247)[c]
Digoxin				
Paritaprevir	1,210 (100)	1,390 (108)	5,660 (95)[d]	6,320 (107)[d]
Ritonavir	2,170 (47)	2,290 (47)	12,600 (49)[c]	12,800 (47)[c]
Ombitasvir	148 (27)	147 (26)	1,430 (27)[d]	1,460 (28)[d]
Digoxin	1.34 (27)	2.16 (19)	27.8 (31)[b]	37.5 (17)[b]
Pravastatin				
Paritaprevir	230 (105)	153 (144)	1,610 (85)[d]	1,300 (119)[d]
Ritonavir	706 (70)	814 (55)	4,420 (53)[d]	5,380 (63)[d]
Ombitasvir	121 (30)	124 (26)	1,020 (25)[d]	1,010 (40)[d]
Pravastatin	18.5 (36)	26.3 (27)	49.4 (30)[d]	86.0 (25)[d]
Rosuvastatin				
Paritaprevir	296 (151)	413 (141)	2,010 (103)[d]	2,450 (83)[d]
Ritonavir	1,110 (56)	1,170 (57)	7,240 (59)[d]	6,780 (57)[d]
Ombitasvir	123 (22)	110 (27)	1,020 (21)[d]	897 (22)[d]
Rosuvastatin	2.33 (45)	6.09 (64)	23.0 (46)[d]	30.7 (46)[d]
Duloxetine				
Paritaprevir	545 (173)	583 (167)	3,450 (190)[d]	3,320 (175)[d]
Ritonavir	925 (72)	975 (59)	5,640 (80)[d]	6,220 (63)[d]
Ombitasvir	112 (36)	116 (41)	1,340 (36)[d]	1,400 (38)[d]
Duloxetine	38 (38)	32 (51)	648 (41)[b]	519 (55)[b]
Escitalopram				
Paritaprevir	455 (93)	540 (45)	2,700 (66)[d]	2,760 (41)[d]
Ritonavir	1,170 (46)	1,620 (29)	6,780 (42)[d]	8,450 (25)[d]
Ombitasvir	111 (28)	128 (26)	1,270 (22)[d]	1,310 (19)[d]
Escitalopram	9.19 (28)	8.86 (21)	262 (32)[b]	209 (35)[b]
S-Desmethylcitalopram	1.51 (26)	1.77 (26)	153 (16)[b]	167 (11)[b]
Methadone[e]				
Paritaprevir	ND	218 (167)	ND	1,300 (145)[d]
Ritonavir	ND	1,460 (37)	ND	9,970 (31)[d]
Ombitasvir	ND	90.9 (37)	ND	1,080 (37)[d]
R-Methadone	3.60 (22)[f]	3.37 (16)[f]	60.9 (25)[d,g]	58.9 (17)[d,g]
S-Methadone	4.76 (31)[f]	4.49 (33)[f]	71.7 (37[d,g]	68.6 (43)[d,g]

(Continued on following page)

TABLE 2 (Continued)

Study	C_{max} (ng/ml)		AUC (ng · h/ml)	
	Alone	Coadministration	Alone	Coadministration
Buprenorphine-naloxone[h]				
Paritaprevir	ND	756 (123)	ND	3,090 (109)[d]
Ritonavir	ND	1,690 (27)	ND	9,860 (31)[d]
Ombitasvir	ND	97.5 (25)	ND	1,020 (29)[d]
Buprenorphine	642 (43)[i]	764 (38)[i]	4,610 (46)[d,j]	6,940 (38)[d,j]
Norbuprenorphine	416 (47)[i]	758 (61)[i]	6,530 (45)[d,j]	13,800 (56)[d,j]
Naloxone	59.0 (44)[i]	58.1 (61)[i]	139 (53)[d,j]	154 (76)[d,j]

[a] Values shown are geometric means (%CV). $n = 10–12$ for each value.
[b] AUC_{∞}.
[c] $AUC_{0\text{-}24}$.
[d] AUC_{tau} (AUC_{24}).
[e] Methadone dose (mean ± SD): 67.1 mg ± 30.0 mg. ND, not determined: all subjects were receiving methadone upon enrollment in the study; therefore, pharmacokinetic parameters in the absence of this medication are not available.
[f] Dose normalized (ng/ml/mg).
[g] Dose normalized (ng · h/ml/mg).
[h] Buprenorphine and naloxone doses, median (range): buprenorphine, 12 mg (4–16 mg); naloxone, 3 mg (1–4 mg). Norbuprenorphine exposures were dose normalized using the buprenorphine dose. ND, not determined: all subjects were receiving buprenorphine-naloxone upon enrollment in the study; therefore, pharmacokinetic parameters in the absence of these medications are not available.
[i] Dose normalized (pg/ml/mg).
[j] Dose normalized (pg · h/ml/mg).

(iii) T_{max} and $t_{1/2}$. The values for T_{max} and $t_{1/2}$ (where calculated) for ombitasvir, paritaprevir, ritonavir, or the interacting medications were not affected in a meaningful way, except in the ketoconazole study, as described earlier.

Safety. Four subjects experienced adverse events that led to premature discontinuation from the studies. One subject in the warfarin study experienced an adverse event of rhabdomyolysis that was considered by the investigator to have a reasonable possibility of being related to the 2D regimen. This subject's creatine phosphokinase (CPK) level was elevated at screening and continued to be elevated after the single dose of warfarin and prior to initiation of the 2D regimen. The CPK level temporarily declined upon administration of the 2D regimen but then increased significantly, which led to discontinuation of the 2D regimen. The subject was not taking any other medications. The elevation/fluctuation of CPK in this subject before 2D administration suggests that causes other than the 2D therapy may have precipitated the event. The subject was referred to a rheumatologist but did not keep the appointment and was lost to follow-up. One subject in the statin study experienced vomiting during coadministration of pravastatin and the 2D regimen. The event of vomiting resolved without intervention after the study drugs were discontinued and was considered by the investigator to have a reasonable possibility of being related to the 2D regimen. The third subject (escitalopram-duloxetine study) experienced an adverse event of lobar pneumonia and a serious adverse event of bacterial prostatitis, both of which were considered by the investigator to have no reasonable possibility of being related to the 2D regimen. The study drugs were discontinued, and the events resolved upon treatment. The fourth subject discontinued from the study after receiving a single dose of digoxin, but before receiving the 2D regimen, due to an asymptomatic adverse event of elevated alanine aminotransferase.

Across the studies, no clinically meaningful changes in physical examination findings, vital sign values, electrocardiogram parameters, or other laboratory values were observed.

DISCUSSION

The potential for drug-drug interactions with the 2D regimen of ombitasvir and paritaprevir-ritonavir was determined from mechanistic, *in vivo* evaluations using probe substrates and inhibitors and evaluations of medications likely to be coprescribed in HCV-infected patients. The evaluations were conducted with the 2-DAA combination (2D) regimen, rather than with the individual DAAs, to provide findings that would be clinically relevant. Drug-drug interactions are of particular concern in HCV-infected patients because these interactions may increase the frequency or severity of adverse events, potentially resulting in poor treatment compliance and the emergence of viral resistance. In a study of 135 HCV genotype 4-infected patients receiving the 2D regimen with or without ribavirin, the most commonly reported adverse events were asthenia, fatigue, nausea, insomnia, pruritus, and skin reactions (19).

In the current studies, the changes in the DAA exposures from the 2D regimen were limited (≤51%), except for the increase in paritaprevir exposures observed upon coadministration with ketoconazole (up to 116% increase). In phase 2 studies, higher doses (200 mg, $n = 85$, or 250 mg, $n = 19$) of paritaprevir have shown acceptable safety profiles (20, 21). These doses provided exposures approximately 93% higher (200 mg) and 250% higher (250 mg) than those observed with the 150-mg paritaprevir dose administered in the current studies (22). The changes in ombitasvir exposures in the presence of the concomitant medications ranged from a 12% lower C_{max} with rosuvastatin to a 26% higher AUC with ketoconazole. Ombitasvir doses of 5 mg to 200 mg have been evaluated with pegylated interferon alpha-2a plus ribavirin for 12 weeks in 23 HCV genotype 1-infected patients (23). The safety and efficacy profiles across these 5-fold lower and 8-fold higher ranges of exposures were comparable to those observed with the 25-mg dose of ombitasvir. No dose adjustment is required for ombitasvir and paritaprevir-ritonavir based on the drug interactions evaluated with the 2D regimen.

TABLE 3 Dosing recommendations from mechanism-based drug-drug interaction studies[a]

Mechanism evaluated	Probe substrate or inhibitor	Recommendation when coadministered with the 2D regimen
CYP3A and P-gp inhibition	Ketoconazole	Limit ketoconazole and itraconazole doses to ≤200 mg/day. Lower doses are recommended for posaconazole.
CYP2C9 inhibition	Warfarin	No dose adjustment is required for warfarin; routine international normalized ratio (INR) monitoring is recommended. No interaction is expected for the other CYP2C9 substrates (e.g., NSAIDS[b] including celecoxib and ibuprofen and antidiabetics including glimepiride, glipizide, and tolbutamide).
CYP2C19 inhibition/induction and effect of acid-reducing agents	Omeprazole	No *a priori* dose adjustment is required; increase the dose if clinically indicated for omeprazole and other CYP2C19 substrates (e.g., lansoprazole, esomeprazole, and pantoprazole).
P-gp inhibition	Digoxin	Reduce the digoxin dose by 30% to 50%; routine therapeutic drug monitoring is recommended. Lower doses are recommended for other P-gp substrates (e.g., talinolol).
OATP1B1/B3 inhibition	Pravastatin	Reduce the pravastatin dose by half; lower doses are recommended for other OATP1B1/B3 substrates (e.g., angiotensin II receptor blockers including valsartan, olmesartan, and telmisartan and statins including pitavastatin and fluvastatin).
OATP1B1/B3 and BCRP inhibition	Rosuvastatin	Reduce the rosuvastatin dose by half; lower doses are recommended for other BCRP substrates (e.g., sulfasalazine).

[a] Consult approved local labels for country-specific dosing recommendations.
[b] NSAIDs, nonsteroidal anti-inflammatory drugs.

Ribavirin is administered with the 2D regimen for HCV infection with either genotype 2 or genotype 4. Ribavirin does not share common disposition pathways with the DAAs and is not expected to contribute to the DAA drug interactions. Furthermore, the duration of dosing in the current drug-drug interaction studies ranged from 2 to 4 weeks. Given the toxicity of ribavirin, it was not deemed appropriate to give ribavirin to healthy subjects for these durations, especially because an interaction was not expected.

For the interacting medications, the clinical relevance of the magnitude of interaction was determined based on data from package inserts, regulatory documents, or literature. Dosing recommendations for medications evaluated in these studies and other medications with similar metabolic/transporter pathways were developed for HCV-infected patients (Tables 3 and 4) and are discussed below.

Mechanism-based drug-drug interactions. In the drug-drug interaction study with the potent CYP3A (and P-gp) inhibitor, ketoconazole, minimal to modest increases in paritaprevir, ombitasvir, and ritonavir exposures and paritaprevir and ombitasvir half-lives were observed. These increases do not necessitate dose adjustments for ombitasvir or paritaprevir-ritonavir. However, the dose of ketoconazole should be limited to 200 mg/day or less due to the 105% increase in the AUC and the 4-fold longer half-life.

TABLE 4 Dosing recommendations based on drug-drug interactions with commonly used medications[a]

Drug class	Medication	Recommendation when coadministered with the 2D regimen
Antiaddictives	Methadone	No dose adjustment
	Buprenorphine	No dose adjustment
	Naloxone	No dose adjustment
Antidepressants	Escitalopram	No dose adjustment for escitalopram or citalopram
	Duloxetine	No dose adjustment for duloxetine, fluoxetine, paroxetine, or desipramine

[a] Consult approved local labels for country-specific dosing recommendations.

Exposures of the CYP2C19 substrate, omeprazole, decreased when omeprazole was coadministered with the 2D regimen, which can be attributed to the known CYP2C19 induction by ritonavir (24–26). The reason for the variability in omeprazole exposures in the presence of the 2D regimen is not known, although omeprazole generally exhibits highly variable plasma concentrations. CYP2C19 genotyping (9 extensive metabolizers, 2 intermediate metabolizers, and no poor metabolizers) did not reveal a discernible trend in the exposure data among the subjects in the study. Other factors, such as interindividual differences in hepatic intrinsic clearance, may explain the variability (24). Although *a priori* dose modification is not required for omeprazole or other CYP2C19 substrates, higher doses should be considered if clinically indicated.

The study with the CYP2C9 substrate, warfarin, suggests that ombitasvir and paritaprevir-ritonavir do not induce or inhibit CYP2C9. However, routine clinical monitoring is recommended for warfarin. No dose adjustment is required for other broad-therapeutic-index drugs that are CYP2C9 substrates (e.g., nonsteroidal anti-inflammatory drugs like ibuprofen or antidiabetics like glimepiride and glipizide).

In vitro data suggest that paritaprevir and ritonavir are potential inhibitors of P-gp (13). Modest increases in digoxin exposures of 36% to 58% were observed during coadministration with the 2D regimen, suggesting that the 2D regimen inhibits P-gp *in vivo*. As a result, the digoxin dose should be reduced by 30% to 50% and routine therapeutic drug monitoring should be performed for digoxin during coadministration with the 2D regimen. Lower doses are recommended for other P-gp substrates when coadministered with the 2D regimen.

In vitro data also suggest that paritaprevir and ritonavir are BCRP inhibitors and that paritaprevir is an OATP1B1/B3 inhibitor (13). Accordingly, exposures of pravastatin (OATP1B1/B3 substrate) and rosuvastatin (OATP1B1/B3 plus BCRP substrate) showed clinically significant increases. Rosuvastatin exposures in-

creased by 33% to 161%, while pravastatin exposures increased by 43% to 76%. Based on the magnitude of the interactions, the pravastatin and rosuvastatin doses should be reduced by half when the drugs are coadministered with the 2D regimen. Alternatively, the rosuvastatin dose should not exceed 20 mg/day.

Interactions with other commonly used medications. (i) Addiction treatment medications. Patients receiving methadone or buprenorphine-naloxone do not require dose adjustments of these drugs when coadministered with the 2D regimen. Buprenorphine is a substrate of CYP3A4 and UDP glucuronosyltransferase 1A1 (UGT1A1). The DAAs are inhibitors of UGT1A1, and ritonavir causes CYP3A4 inhibition; thus, the increases in the exposures of buprenorphine and its metabolite, norbuprenorphine, may be due to inhibition of CYP3A4 and/or UGT1A1. The increases in buprenorphine and norbuprenorphine exposures were not associated with pharmacodynamic changes.

(ii) Antidepressants. The exposures of escitalopram and its metabolite, *S*-desmethylcitalopram, were minimally affected upon coadministration with the 2D regimen, and no escitalopram dose modification is needed. Escitalopram is a substrate of CYP2C19 and CYP3A4. The 25% decrease in the escitalopram AUC is likely due to ritonavir-mediated CYP2C19 induction that may be partially offset by ritonavir-mediated CYP3A4 inhibition (26). The 17% to 20% decreases in duloxetine exposures do not necessitate dose adjustment, as decreases in duloxetine exposures of up to 30% are not expected to affect efficacy (27).

Although not directly evaluated, the drug-drug interaction study results for carbamazepine, amlodipine, alprazolam, zolpidem, furosemide, oral contraceptives, and gemfibrozil can be inferred for the 2D regimen based on results from treatment arms that received the 3D regimen (11, 18, 19). During coadministration with the 2D regimen, no dose adjustment is needed for gemfibrozil (contraindicated with the 3D regimen due to an interaction with dasabuvir), zolpidem, or norethindrone. No *a priori* dose adjustment is needed for alprazolam or furosemide, but clinical monitoring is recommended because of potentially modest increases in alprazolam exposures due to CYP3A inhibition by ritonavir and modest increases in furosemide exposures due to UGT1A1 inhibition by ombitasvir and paritaprevir. The amlodipine dose should be reduced by half due to increases in amlodipine exposures upon ritonavir-mediated inhibition of CYP3A. Carbamazepine and ethinyl estradiol-containing contraceptives are contraindicated with both the 2D and 3D regimens.

In conclusion, a comprehensive evaluation of drug-drug interactions for the 2D regimen of ombitasvir and paritaprevir-ritonavir and 11 medications was conducted in 8 separate phase 1 studies. These investigations revealed that all of the medications that were evaluated can be coadministered with the 2D regimen, with most medications requiring no dose adjustment. Reduced doses of pravastatin, rosuvastatin, digoxin, and ketoconazole are recommended to offset the increases in exposures observed during coadministration. In addition, higher doses of omeprazole may be required if clinically indicated. These recommendations are summarized in the product labeling (11, 19).

No dose adjustment is required for the 2D regimen when coadministered with any of the medications that are not contraindicated.

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