Research Article

EASL JOURNAL OF HEPATOLOGY



# Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir

Rajeev M. Menon*, Prajakta S. Badri, Tianli Wang, Akshanth R. Polepally, Jiuhong Zha, Amit Khatri, Haoyu Wang, Beibei Hu, Eoin P. Coakley, Thomas J. Podsadecki, Walid M. Awni, Sandeep Dutta

*AbbVie Inc., North Chicago, IL, USA*

**Background & Aims**: Paritaprevir (administered with ritonavir, PTV/r), ombitasvir (OBV), and dasabuvir (DSV) are direct-acting antiviral agents (DAAs) for the treatment of chronic hepatitis C virus (HCV) infection. Thirteen studies were conducted to characterize drug-drug interactions for the 3D regimen of OBV, PTV/r, and DSV and various medications in healthy volunteers to inform dosing recommendations in HCV-infected patients.

**Methods**: Mechanism-based drug-drug interactions were evaluated for gemfibrozil, ketoconazole, carbamazepine, warfarin, omeprazole, digoxin, pravastatin, and rosuvastatin. Drug-drug interactions with medications commonly used in HCV-infected patients were evaluated for amlodipine, furosemide, alprazolam, zolpidem, duloxetine, escitalopram, methadone, buprenorphine/naloxone, and oral contraceptives. Ratios of geometric means with 90% confidence intervals for maximum plasma concentration ($C_{max}$) and area under the plasma concentration-time curve (AUC) were used to determine the magnitude of interaction.

**Results**: Coadministration with the 3D regimen of OBV, PTV/r, and DSV resulted in a <2-fold change in mean $C_{max}$ and AUC for most medications and the DAAs, indicating minimal to modest interactions. Carbamazepine decreased PTV, ritonavir, and DSV exposures substantially, while gemfibrozil increased DSV exposures substantially. Although coadministration with ethinyl estradiol-containing contraceptives resulted in elevated alanine aminotransferase levels, coadministration with a progestin-only contraceptive did not.

**Conclusions**: The majority of medications can be coadministered with the 3D regimen of OBV, PTV/r, and DSV without dose adjustment, or with clinical monitoring or dose adjustment. Although no dose adjustment is necessary for the 3D regimen when coadministered with 17 of the 20 medications, coadministration with gemfibrozil, carbamazepine, or ethinyl estradiol-containing contraceptives is contraindicated.



Keywords: Paritaprevir; Ritonavir; Ombitasvir; Dasabuvir; Drug-drug interactions; Hepatitis C virus.

*Received 25 November 2014; received in revised form 13 January 2015; accepted 20 January 2015*

* Corresponding author. Address: AbbVie Inc., Clinical Pharmacokinetics and Pharmacodynamics, 1 North Waukegan Road, R4PK, AP13A-3, North Chicago, IL 60064, USA. Tel.: +1 (847) 935 9066; fax: +1 (847) 938 5193.

*E-mail address:* Rajeev.menon@abbvie.com (R.M. Menon).

*Abbreviations:* PTV/r, paritaprevir/ritonavir; OBV, ombitasvir; DSV, dasabuvir; DAA, direct-acting antiviral agent; HCV, hepatitis C virus; $C_{max}$, maximum observed plasma concentration; AUC, area under the plasma concentration-time curve; SVR, sustained virologic response; NS, nonstructural; CYP, cytochrome P450; QD, once daily; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; EE, ethinyl estradiol; BID, twice daily; LLOQ, lower limit of quantitation; $T_{max}$, time to maximum observed plasma concentration ($C_{max}$); $C_{trough}$, trough concentration; $t_{1/2}$, terminal phase elimination half-life; GMR, geometric mean ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

## Introduction

The risk of morbidity and mortality related to chronic hepatitis C virus (HCV) infection is markedly reduced in patients who achieve a sustained virologic response (SVR) with antiviral therapy [1–4]. Recently, development of direct-acting antiviral agents (DAAs) targeting various steps in the HCV life cycle has led to substantial improvements in efficacy and reductions in toxicity compared to prior interferon-based therapies. However, judicious use of these DAAs requires strict attention to drug-drug interactions because all HCV combination regimens interact with drug metabolizing enzymes, drug transporters, or both [5]. Knowledge of drug-drug interactions is important for appropriate clinical management, which sometimes requires dose adjustments or discontinuation of contraindicated medications [6,7].

Paritaprevir (ABT-450, PTV) is a nonstructural (NS) protein 3/4A protease inhibitor. PTV is metabolized primarily by cytochrome P450 (CYP) 3A and is given with a low dose of the CYP3A inhibitor, ritonavir, as a pharmacokinetic enhancer to achieve higher peak, trough, and overall PTV exposures. This enables once daily (QD) administration and use of lower PTV doses than would be necessary without ritonavir. The use of ritonavir also limits the potential for further interaction of PTV with other CYP3A inhibitors. Ombitasvir (ABT-267, OBV) is a potent NS5A inhibitor and dasabuvir (ABT-333, DSV) is an NS5B non-nucleoside polymerase inhibitor. Phase 3 clinical trials of the combination of these three DAAs (3D regimen of OBV, PTV/r, and DSV) with and without ribavirin have demonstrated SVR rates 12 weeks after the end of treatment of 92% to 100%, in cirrhotic and noncirrhotic HCV genotype 1-infected subjects [8–11].

*In vitro* data indicate PTV and ritonavir are primarily metabolized by CYP3A, while DSV is primarily metabolized by CYP2C8 [12]. DSV may also undergo metabolism by CYP3A. Ombitasvir



Please cite this article in press as: Menon RM et al. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.01.026

# Research Article

is predominantly metabolized by amide hydrolysis followed by oxidative metabolism. Ritonavir is a CYP3A inhibitor, while the DAAs do not inhibit CYP enzymes. *In vitro* data also suggest that at clinically relevant concentrations, PTV is an organic anion transporting polypeptide (OATP) 1B1/B3 inhibitor and PTV, ritonavir, and DSV are potential inhibitors of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) [12]. The DAAs and ritonavir are *in vitro* substrates of P-gp and BCRP, and PTV is also a substrate of OATP1B1/B3.

A broad drug-drug interaction program was conducted in healthy volunteers to evaluate the potential for interactions with the 3D regimen of OBV, PTV/r, and DSV. These studies characterized mechanism-based interactions and interactions that may occur with medications commonly used in HCV-infected patients. Mechanism-based interactions, which characterize interactions associated with specific enzymes or transporters, were evaluated using standard probe substrates, inhibitors, or inducers. Results from these interactions can be used to predict interactions and provide dosing recommendations for other medications that share the same metabolic and transporter pathways.

Mechanism-based interaction studies evaluated the following enzymes and transporters: CYP2C9 and 2C19 (substrates: warfarin, omeprazole), CYP2C8 (inhibitor: gemfibrozil), CYP3A and P-gp (inhibitor: ketoconazole; inducer: carbamazepine), P-gp (substrate: digoxin), OATP1B1/B3 (substrate: pravastatin), and OATP1B1/B3 plus BCRP (substrate: rosuvastatin). The substrates, inhibitors, and inducers chosen for evaluation were based on regulatory guidance from the United States Food and Drug Administration and the European Medicines Agency [13,14].

Drug-drug interactions with commonly used medications representing the drug classes of antidepressants (escitalopram and duloxetine), antihypertensives (amlodipine), diuretics (furosemide), anxiolytics/sleep aids (alprazolam and zolpidem), and oral contraceptives (norethindrone, ethinyl estradiol [EE] plus norgestimate, and EE plus norethindrone) were studied to assess potential for drug interaction and to provide dosing recommendations for these drugs in patients taking the 3D regimen of OBV, PTV/r, and DSV. Methadone and buprenorphine/naloxone, which are commonly used as opioid substitutions in patients with a history of drug addiction, were also evaluated.

## Materials and methods

### *Study designs*

Thirteen open-label, Phase 1 clinical studies were conducted at five clinical study sites in accordance with Good Clinical Practice guidelines and ethical principles that have their origin in the Declaration of Helsinki. All study protocols and amendments were approved by the institutional review boards at each site and written informed consent was obtained from each subject before any study-related procedures were performed.

Enrolled subjects were healthy adult male or female volunteers, between the ages of 18 and 55 years, with a body mass index between 18 and 30 $kg/m^2$. Metabolic enzyme and drug transporter inhibitors or inducers were not allowed

**Table 1. Medications evaluated in drug-drug interaction studies with the 3D regimen of OBV, PTV/r, and DSV.**

| Mechanism-based drug interactions | | | |
|---|---|---|---|
| Drug class | N | Medication (dose) | Mechanism |
| Antihyperlipidemics | 12 | Gemfibrozil* (600 mg BID) | Effect of CYP2C8 inhibition by gemfibrozil on PTV/r and DSV |
| Antifungals | 12 | Ketoconazole (400 mg QD) | Effect of CYP3A and P-gp inhibition by ketoconazole on 3D |
| Anticonvulsants | 12 | Carbamazepine (200 mg QD and BID) | Effect of CYP3A induction by carbamazepine on 3D |
| Anticoagulants | 12 | Warfarin (5 mg) | Effect of CYP2C9 inhibition/induction by 3D on warfarin |
| Acid reducing agents | 12 | Omeprazole (40 mg QD) | Effect of CYP2C19 inhibition/induction by 3D on omeprazole |
| Antiarrhythmics | 12 | Digoxin (0.5 mg) | Effect of P-gp inhibition by 3D on digoxin |
| Statins | 12 | Pravastatin (10 mg QD) | Effect of OATP1B1/B3 inhibition by 3D on pravastatin |
| | 12 | Rosuvastatin (5 mg QD) | Effect of OATP1B1/B3 + BCRP inhibition by 3D on rosuvastatin |
| Drug interactions with commonly used medications | | | |
| Drug class | N | Medication (metabolic pathway) (dose) | |
| Anti-addictives | 12 | Methadone (CYP3A4/CYP2B6 substrate) (individualized QD dosing 20 to 120 mg per physician's prescription) | |
| | 13 | Buprenorphine/naloxone (CYP3A4; UGT1A1 substrate/UGT substrate) (individualized QD dosing 4/1 mg to 24/6 mg per physician's prescription) | |
| Antidepressants | 12 | Escitalopram (CYP3A4/CYP2C19 substrate) (10 mg) | |
| | 12 | Duloxetine (CYP2D6/CYP1A2 substrate and CYP1A2 inhibitor) (60 mg) | |
| Antihypertensives | 14 | Amlodipine (CYP3A4 substrate) (5 mg) | |
| Anxiolytics/sleep aids | 12 | Alprazolam (CYP3A4 substrate) (0.5 mg) | |
| | 12 | Zolpidem (CYP3A4 substrate) (5 mg) | |
| Diuretics | 12 | Furosemide (UGT1A1 substrate) (20 mg) | |
| Oral contraceptives | 12 | Norethindrone (UGT/CYP3A4/sulfo-transferases substrate) (0.35 mg) | |
| | 9 | Ethinyl estradiol + norgestimate† (UGT/CYP3A4/sulfo-transferases substrate) (35 μg/0.250 mg) | |
| | 12 | Ethinyl estradiol + norethindrone (UGT/CYP3A4/sulfo-transferases substrate) (35 μg/0.4 mg) | |

UGT, uridine diphospho-glucuronosyltransferase; QD, once daily; BID, twice daily.
*Evaluated with a PTV/r + DSV regimen only.
†Evaluated with PTV/r, OBV ± DSV regimens.



Please cite this article in press as: Menon RM et al. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.01.026

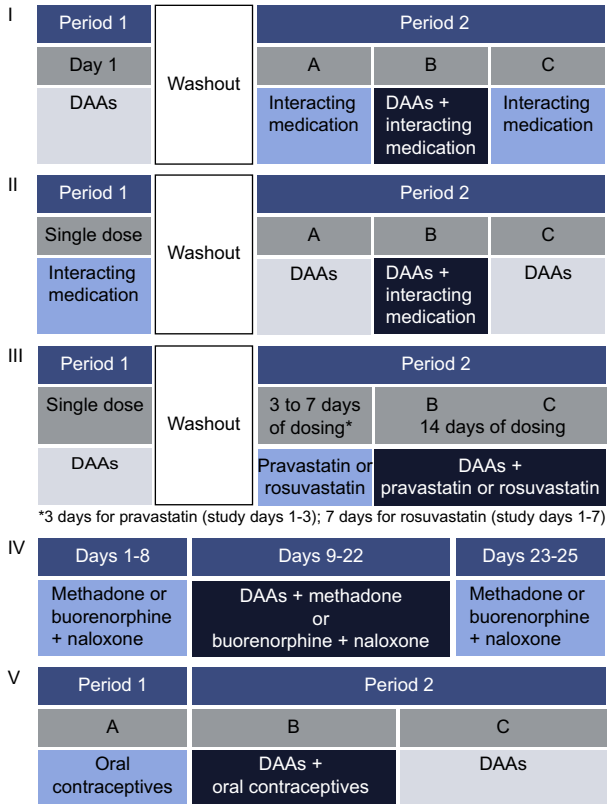


**Fig. 1. Study designs used for evaluating the 20 drug interactions.** For more details on the study designs, refer to Table 2.

within one month of enrollment. Subjects enrolled in the methadone and buprenorphine/naloxone studies were on stable methadone and buprenorphine/naloxone maintenance therapy, respectively, for a minimum of 14 days before the screening visit.

Drug-drug interactions were evaluated for the 3D regimen of OBV, PTV/r, and DSV using 20 drugs from a wide variety of drug classes (Table 1). The doses of PTV/r and OBV were 150 mg/100 mg and 25 mg, respectively and the dose of DSV was 250 mg or 400 mg (Phase 2 formulation), which provided comparable DSV exposures. The regimen evaluated in these studies is the same as that tested in Phase 3 clinical trials for treatment of HCV genotype 1 infection.

Most evaluations were conducted under multiple dosing conditions (PTV/r and OBV QD and DSV twice daily [BID]), although a few mechanism-based interactions were evaluated under single dosing conditions (Fig. 1 and Table 2). For all evaluations, the 3D regimen was coadministered with the interacting drug after a moderate-fat meal (approximately 1900 to 2300 calories/day with 40% of calories from fat).

Key elements of the study designs are presented in Fig. 1 and Table 2. All evaluations were conducted with the 3D regimen of OBV, PTV/r, and DSV except for the study with gemfibrozil, which evaluated interactions only with PTV/r plus DSV. OBV and gemfibrozil are not expected to interact with each other as their metabolic pathways do not overlap.

*Safety and tolerability assessments*

Safety and tolerability were assessed throughout each study based on adverse event monitoring, vital signs measurements, physical examinations, electrocardiogram assessments, and laboratory tests.

*Pharmacokinetic assessments*

Blood samples for determination of plasma concentrations of PTV, ritonavir, OBV, DSV, DSV metabolite M1, and the interacting medications and their metabolites, if applicable, were collected by venipuncture. Plasma concentrations were determined using validated liquid chromatography with tandem mass spectrometric detection methods. The lower limits of quantitation (LLOQs) for PTV, ritonavir, OBV, DSV, and DSV M1 were approximately 0.6 ng/ml, 4.7 ng/ml, 0.4 ng/ml, 4.4 ng/ml, and 4.6 ng/ml, respectively. The LLOQs for the concomitant

**Table 2. Dosing days in different study periods in Fig. 1.**

| | | Days of dosing | | |
|---|---|---|---|---|
| Study design* | Medication | A | B | C |
| I | Gemfibrozil† | Days 4-5 | Day 6 | Days 7-8 |
| I | Ketoconazole | Days 8-9 | Day 10 | Days 11-13 |
| I | Carbamazepine | Days 1-3 (QD)<br>Days 4-21 (BID) | Day 22 | Days 23-24 (BID) |
| II | Digoxin | Days 11-24 | Day 25 | Days 26-29 |
| II | Warfarin | Days 15-28 | Day 29 | Days 30-38 |
| II | Furosemide | Days 3-16 | Day 17 | Day 18 |
| II | Amlodipine | Days 11-24 | Day 25 | Days 26-34 |
| II | Escitalopram | Days 7-20 | Day 21 | Days 22-26 |
| II | Duloxetine | Days 7-20 | Day 21 | Day 22 |
| II | Alprazolam | Days 4-17 | Day 18 | Days 19-21 |
| II | Zolpidem | Days 3-16 | Day 17 | Day 18 |
| II | Omeprazole | Days 6-19 | Days 20-24 | n.a. |
| V | EE/NGM‡ | Days 1-9 | Days 10-21 | Days 22-28 |
| V | EE/NET | Days 1-7 | Days 8-21§ | Days 22-28 |
| V | NET | Days 1-3 | Days 4-17 | Days 18-24 |

QD, once daily; BID, twice daily; EE/NGM, ethinyl estradiol and norgestimate; EE/NET, ethinyl estradiol and norethindrone; NET, norethindrone; n.a., not applicable.
*See Fig. 1.
†Evaluated with a PTV/r + DSV regimen only.
‡Evaluated with PTV/r, OBV ± DSV regimens.
§Study drug discontinued on Day 15.



Please cite this article in press as: Menon RM et al. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.01.026

medications were 0.003 ng/ml (EE), 0.01 ng/ml (digoxin), 0.02 ng/ml (naloxone, norelgestromin, norgestrel), 0.05 ng/ml (amlodipine, S-desmethylcitalopram), 0.1 ng/ml (alprazolam, buprenorphine, norbuprenorphine, ketoconazole, norethindrone, rosuvastatin), 0.2 ng/ml (escitalopram), 0.25 ng/ml (zolpidem), 0.5 ng/ml (duloxetine, pravastatin), 1 ng/ml (R- and S-methadone, omeprazole), 5 ng/ml (R- and S-warfarin, furosemide), and 50 ng/ml (carbamazepine, carbamazepine-10-11-epoxide). For digoxin, urine was also collected and the excreted fraction of drug was measured (LLOQ of 2 ng/ml).

Pharmacokinetic analyses were performed by noncompartmental methods using Phoenix®WinNonlin®Version 6.0 or above (Certara,®St. Louis, MO). The primary pharmacokinetic parameters were maximum observed plasma concentration ($C_{max}$) and area under the plasma concentration-time curve (AUC) during a dosing interval ($AUC_{12}$ for BID administration; $AUC_{24}$ for QD administration) or from time zero to infinity ($AUC_{\infty}$ for single dose). Additional pharmacokinetic parameters include: time to $C_{max}$ ($T_{max}$), trough concentration ($C_{trough}$), and terminal phase elimination half-life ($t_{1/2}$).

*Pharmacodynamic assessments*

For the methadone and buprenorphine/naloxone interaction studies, pharmacodynamic measurements were performed to monitor for signs of withdrawal triggered by possible changes in methadone and buprenorphine/naloxone exposures, during coadministration with OBV, PTV/r, and DSV. Pupil diameter and two self-administered instruments (short opiate withdrawal scale score and the desire for drugs questionnaire) were measured at various time points before and during coadministration.

*Statistical analyses*

Statistical analyses were conducted using SAS, Version 9.2 (Cary, NC). Effects of the 3D regimen of OBV, PTV/r, and DSV on the interacting medications and *vice versa* were estimated by analyzing $log_e$-transformed $C_{max}$ and AUC values under a repeated measures analysis framework. Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for $C_{max}$ and AUC were calculated to quantify the magnitude of interaction.

## Results

*Subject demographics*

A total of 228 subjects, 67% of whom were male, received at least one dose of study drug. Across studies, 64.0% of subjects were white, 31.6% were black, and 4.4% were other races. Demographics of subjects across the 13 studies were similar: the age of subjects ranged from 20 to 55 years, mean age ranged from 29.5 to 39.1 years, and median body weight ranged from 67.6 to 83.7 kg.

*Pharmacokinetics*

*Mechanism-based drug-drug interactions*

Results from studies of mechanism-based interactions of substrates/inhibitors/inducers of CYPs and transporters on DAA and ritonavir exposures and vice versa are shown in Figs. 2 and 3 and discussed below.

*CYP2C8 inhibitor (gemfibrozil)*

Coadministration of PTV/r plus DSV with gemfibrozil did not affect exposures of ritonavir, but increased PTV $C_{max}$ and AUC (21% and 38%, respectively) as well as DSV $C_{max}$ and AUC (101% and 1030%, respectively). The mean $t_{1/2}$ of DSV increased from approximately 5 to 90 h. In contrast to the increase in DSV exposures, $C_{max}$ and AUC values of DSV metabolite M1 decreased, with 95% lower $C_{max}$ and 78% lower AUC values.

*CYP3A and P-gp inhibitor (ketoconazole)*

In the presence of ketoconazole, increased $C_{max}$ and AUC values were observed for PTV (37% and 98%, respectively) and ritonavir (27% and 57%, respectively) and an increased AUC value was observed for DSV (42%). DSV $C_{max}$ (16% increase) and OBV $C_{max}$ and AUC ($\leqslant$17% change) were not affected. The mean $t_{1/2}$ of PTV was 2-fold longer (13.7 *vs.* 5.5 h) in the presence of ketoconazole.

Ketoconazole $C_{max}$ was not affected (15% increase), but ketoconazole AUC increased by 117%. The mean $t_{1/2}$ of ketoconazole was 4-fold longer (15.7 *vs.* 3.3 h) in the presence of OBV, PTV/r, and DSV.

*CYP3A and P-gp inducer (carbamazepine)*

When the 3D regimen of OBV, PTV/r, and DSV was coadministered with carbamazepine, decreased $C_{max}$ and AUC values were observed for PTV (66% and 70%, respectively), DSV (55% and 70%, respectively) and ritonavir (83% and 87%, respectively), and to a lesser extent, OBV (31% and 30%, respectively) and DSV metabolite M1 (36% lower AUC).

Carbamazepine $C_{max}$ and AUC values were not affected ($\leqslant$17% change), but the metabolite carbamazepine-10, 11-epoxide AUC value decreased by 25%.

*CYP2C9 substrate (warfarin)*

Coadministration with the 3D regimen of OBV, PTV/r, and DSV did not affect R- or S-warfarin exposures ($\leqslant$12% change in $C_{max}$ and AUC) or PTV, ritonavir, OBV, DSV exposures ($\leqslant$7% change in $C_{max}$ and AUC).

*CYP2C19 substrate (omeprazole)*

In the presence of the 3D regimen of OBV, PTV/r, and DSV, the $C_{max}$ and AUC values of omeprazole were reduced by 38%, but PTV, ritonavir, OBV, and DSV exposures were relatively unchanged ($\leqslant$19% change in $C_{max}$ and AUC).

*P-gp substrate (digoxin)*

During coadministration with the 3D regimen of OBV, PTV/r, and DSV, values for digoxin $C_{max}$ and AUC ($\leqslant$16% increase), $C_{24}$ (1% change), and the fraction of unchanged drug eliminated in the urine (ratio of fraction excreted: 0.98) were essentially unchanged, as were PTV, ritonavir, OBV, and DSV exposures ($\leqslant$8% change in $C_{max}$ and AUC).

*OATP1B1/B3 substrate (pravastatin)*

Coadministration of pravastatin with the 3D regimen of OBV, PTV/r, and DSV increased pravastatin $C_{max}$ and AUC values by 37% and 82%, respectively, but did not affect PTV, ritonavir, OBV, or DSV exposures ($\leqslant$13% change in $C_{max}$ and AUC).

*OATP1B1/B3 and BCRP substrate (rosuvastatin)*

Rosuvastatin exposures increased in the presence of the 3D regimen of OBV, PTV/r, and DSV: $C_{max}$ increased by 613% and AUC increased by 159%. PTV $C_{max}$ and AUC increased by 59% and 52%, respectively, but ritonavir, OBV, and DSV exposures were unaffected ($\leqslant$11% change in $C_{max}$ and AUC).



Please cite this article in press as: Menon RM et al. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.01.026

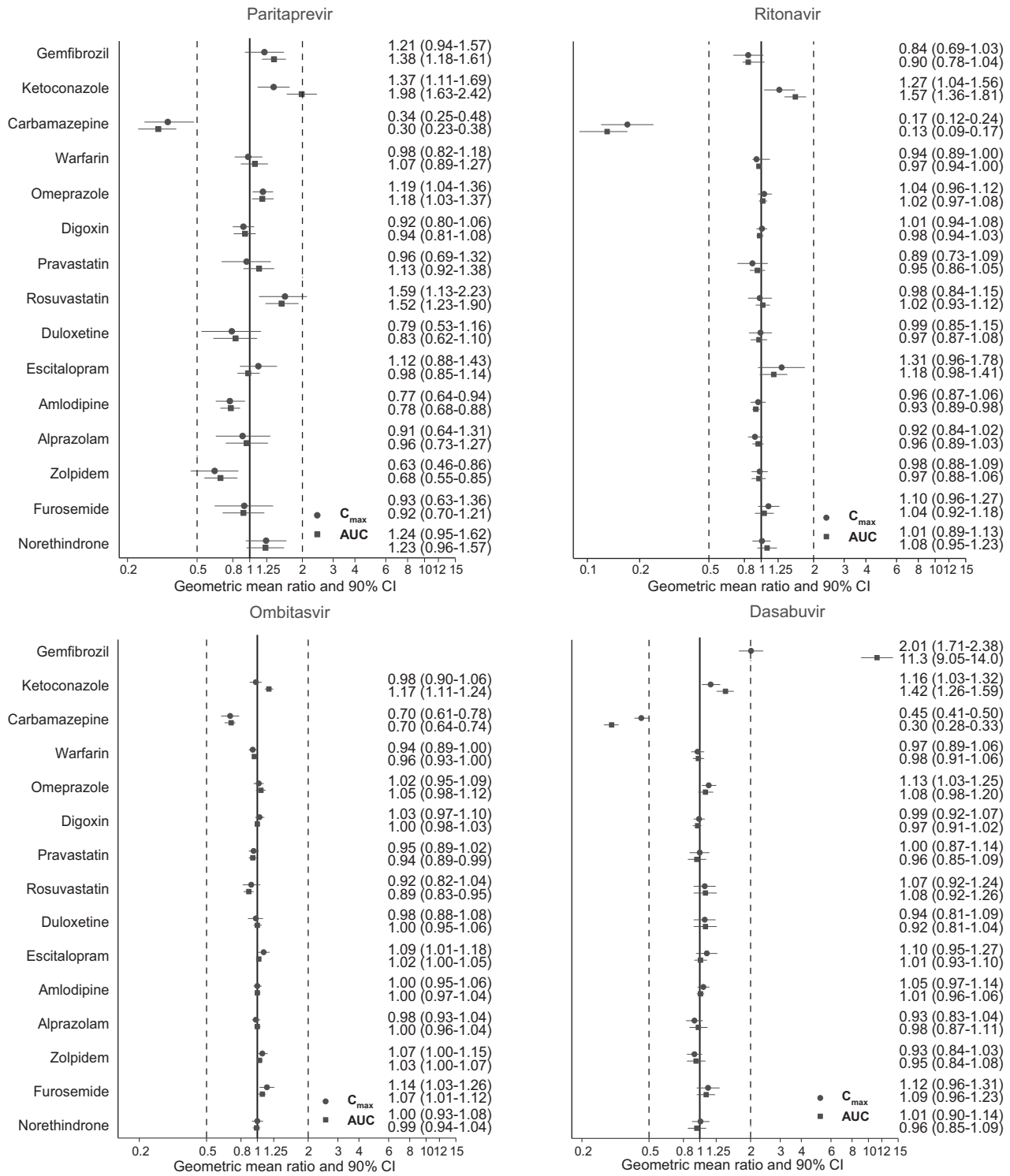


**Fig. 2. Effect of concomitant medications on the $C_{max}$ and AUC values of PTV, ritonavir, OBV, and DSV (geometric mean ratio and 90% CI).** GMR indicate $C_{max}$ and AUC values for coadministration of the medication with the 3D regimen *vs.* administration of the 3D regimen alone. For gemfibrozil, a PTV/r + DSV regimen was evaluated.

*Interactions with commonly used medications*

Effects of the 3D regimen of OBV, PTV/r, and DSV on exposures of medications commonly used in HCV-infected patients are presented in Fig. 3, and effects of these commonly used medications on the exposures of the DAAs and ritonavir are presented in Fig. 2.

*Addiction treatment medications (methadone and buprenorphine/naloxone)*

Coadministration of the 3D regimen of OBV, PTV/r, and DSV with methadone did not affect R- or S-methadone exposures (⩽5%



Please cite this article in press as: Menon RM et al. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.01.026

# Research Article

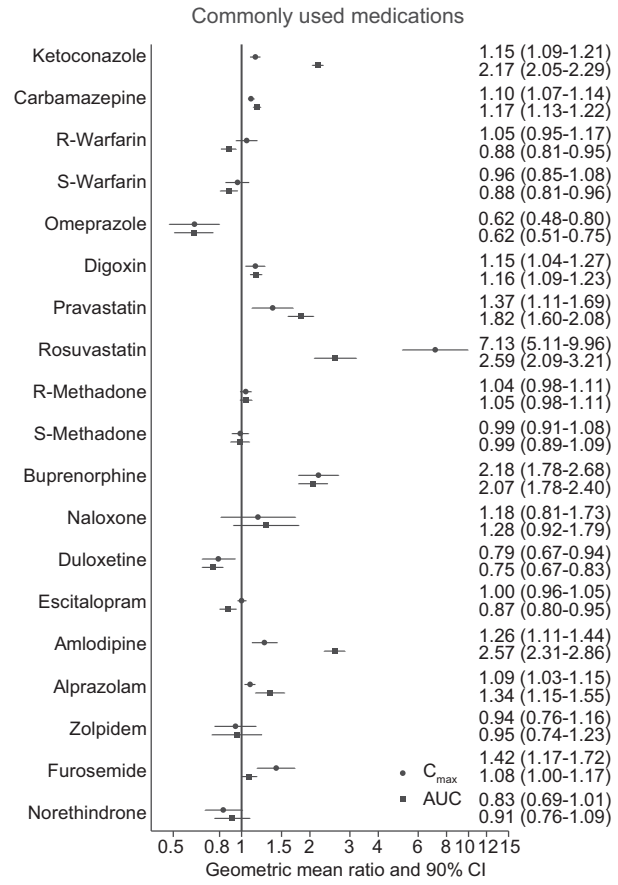


**Fig. 3. Effect of the 3D regimen of OBV, PTV/r, and DSV on the $C_{max}$ and AUC values of concomitant medications (geometric mean ratio and 90% CI).** GMR indicate $C_{max}$ and AUC values for coadministration of the medication with the 3D regimen *vs.* administration of the medication alone.

change in $C_{max}$ and AUC). Coadministration had a modest effect on naloxone exposures (18% and 28% increase in $C_{max}$ and AUC, respectively). In contrast, buprenorphine $C_{max}$ and AUC increased by 118% and 107%, respectively, and norbuprenorphine $C_{max}$ and AUC increased by 107% and 84%, respectively, upon coadministration. Results from pharmacodynamic measurements indicated no significant changes in pupil diameter, opioid withdrawal scale score, or desire for drug questionnaire score when methadone or buprenorphine/naloxone was administered with the 3D regimen, compared to methadone or buprenorphine/naloxone dosed alone.

Geometric mean values of $C_{max}$ and AUC for PTV, ritonavir, OBV, and DSV in these studies were comparable to those observed when the 3D regimen was administered alone in studies evaluating interactions with duloxetine, escitalopram, alprazolam, and furosemide.

*Antidepressants (escitalopram and duloxetine)*

In the presence of the 3D regimen of OBV, PTV/r, and DSV, escitalopram exposures were not affected (no change in $C_{max}$ and 13% decrease in AUC); however, the AUC of metabolite S-desmethyl citalopram increased by 36%. Coadministration reduced duloxetine $C_{max}$ and AUC by 21% and 25%, respectively, but did not affect DAA or ritonavir exposures, except for a 21% decrease in PTV $C_{max}$ in the presence of duloxetine and a 31% increase in ritonavir $C_{max}$ in the presence of escitalopram.

*Antihypertensive calcium channel blocker (amlodipine)*

Coadministration of amlodipine with the 3D regimen of OBV, PTV/r, and DSV increased amlodipine $C_{max}$ and AUC by 26% and 157%, respectively, and decreased PTV $C_{max}$ and AUC by 23% and 22%, respectively. Ritonavir, OBV, and DSV exposures were unaffected ($\leqslant$7% change in $C_{max}$ and AUC).

*Anxiolytic/sleep aid (alprazolam and zolpidem)*

When coadministered with the 3D regimen of OBV, PTV/r, and DSV, zolpidem exposures did not change ($\leqslant$6% decrease in $C_{max}$ and AUC), alprazolam $C_{max}$ was not affected (9% increase), and alprazolam AUC increased by 34%. DAA and ritonavir exposures were unaffected by alprazolam or zolpidem ($\leqslant$9% change in $C_{max}$ and AUC), except for 37% and 32% decreases in PTV $C_{max}$ and AUC, respectively, in the presence of zolpidem.

*Diuretic (furosemide)*

In the presence of the 3D regimen of OBV, PTV/r, and DSV, furosemide $C_{max}$ increased by 42% though furosemide AUC was not affected (8% increase). Furosemide had minimal impact ($\leqslant$14% change in $C_{max}$ and AUC) on PTV, ritonavir, OBV, and DSV exposures.

*Oral contraceptives*

Three oral contraceptives were evaluated with the 3D regimen of OBV, PTV/r, and DSV in the same study: one containing progestin-only (norethindrone) and two containing a combination of EE and a progestin (norgestimate or norethindrone). EE plus norgestimate was also administered with PTV/r and OBV (without DSV). Enrollment in the EE plus norgestimate arms was stopped due to safety concerns after enrolling only three subjects in the OBV, PTV/r, and DSV regimen and six subjects in the regimen without DSV. Data from these nine subjects were combined for analyses.

Coadministration of the 3D regimen of OBV, PTV/r, and DSV with norethindrone did not affect norethindrone, ritonavir, OBV, or DSV exposures ($\leqslant$17% change in $C_{max}$ and AUC), but increased PTV $C_{max}$ and AUC by 24% and 23%, respectively.

Norelgestromin, a metabolite of norgestimate, $C_{max}$ and AUC values increased by 101% and 160%, respectively, and norgestrel, another metabolite of norgestimate, $C_{max}$ and AUC values increased by 126% and 154%, respectively. Coadministration did not affect exposures of EE ($\leqslant$16% change in $C_{max}$ and AUC) or OBV ($\leqslant$5% change in $C_{max}$ and AUC), but decreased PTV and ritonavir exposures by up to 34% and decreased DSV exposures by approximately 52%.

For EE plus norethindrone, coadministration with the 3D regimen of OBV, PTV/r, and DSV did not affect EE $C_{max}$ (17% increase), but increased EE AUC by 22%. Similarly, norethindrone $C_{max}$ was not affected (12% increase), but AUC was increased by 29%. Since the study was stopped prior to availability of steady-state interaction data, these results are based on data available following the first day of co-dosing.



Please cite this article in press as: Menon RM et al. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.01.026

*$T_{max}$, $T_{1/2}$ and DSV metabolite M1 pharmacokinetics*

Across the 13 studies, $T_{max}$ and $t_{1/2}$ (where calculated) values for the interacting drugs or DAAs were not affected in a meaningful way, except in the ketoconazole and gemfibrozil studies, as described earlier. In addition, DSV metabolite M1 exposures mirrored DSV exposures except for the interaction with gemfibrozil, in which DSV exposures increased and DSV M1 exposures decreased, and the interaction with carbamazepine, where DSV M1 exposures decreased to a lesser extent than DSV exposures.

*Safety*

There were no serious adverse events with the 3D regimen of OBV, PTV/r, and DSV in any of the studies. In studies other than the oral contraceptives study discussed below, 2 subjects discontinued study drug due to an adverse event: one due to aspartate aminotransferase (AST) elevation and one due to pruritus. The adverse event of AST elevation occurred in a subject who received a single 10 mg dose of escitalopram on Study Days 1 and 21 and the 3D regimen on Study Days 7 through 21. The maximum increase in AST (199 U/L) occurred on Day 21, at which time the subject was discontinued from study drug. AST levels returned to normal on Day 26. The adverse event of pruritus occurred on Study Day 1, 3 h after the subject received a single dose of PTV/r plus DSV in the gemfibrozil study. Study drug was discontinued, the subject was treated with oral diphenhydramine, and the event resolved on Study Day 6.

In the oral contraceptive study, among subjects who received the 3D regimen of OBV, PTV/r, and DSV and norethindrone, no subject prematurely discontinued study drug or experienced Grade 2 or greater alanine aminotransferase (ALT) elevations. In subjects who received EE plus norgestimate or norethindrone, 5 of 21 subjects experienced Grade 3/4 ALT elevations. Four of the five subjects with these adverse events prematurely discontinued study drug and the fifth subject (on EE plus norethindrone) discontinued study drug when the study arm was stopped on Day 15. The ALT elevations in these subjects normalized after dosing was stopped. In all of these subjects, the ALT elevations were asymptomatic and there were no concurrent bilirubin elevations $\geqslant$2 times the upper limit of normal.

Across studies, no clinically meaningful changes in vital signs values, electrocardiogram parameters, or other laboratory values were observed.

## Discussion

The potential for interactions with the 3D regimen of OBV, PTV/r, and DSV was ascertained from mechanistic, *in vivo* evaluations using probe substrates/inhibitors/inducers and evaluations of medications likely to be coprescribed in HCV-infected patients. Evaluations were conducted with the DAA combination regimen, rather than with the individual DAAs, to provide findings that would be clinically relevant.

Lower and higher doses of PTV, OBV, and DSV have been evaluated in HCV-infected subjects that confirm that the changes in exposures observed with comedications (except carbamazepine and gemfibrozil) in the current studies are not clinically meaningful. The maximum changes in PTV exposures were observed with ketoconazole (~100% higher) and zolpidem (~40% lower). In Phase 2 studies, lower (100 mg) and higher (200 or 250 mg) doses of PTV have been shown to have comparable efficacy and acceptable safety profiles [15,16]. These doses provided exposures 55% lower (100 mg), 93% higher (200 mg), and 250% higher (250 mg) than those observed with the 150 mg PTV dose administered [17].

Changes in OBV exposures in the presence of the concomitant medications ranged from 11% lower with rosuvastatin to 17% higher with ketoconazole. OBV doses of 5 mg to 200 mg have been evaluated with peg-interferon plus ribavirin for 12 weeks [18]. The safety and efficacy profiles across this 5-fold lower and 8-fold higher range of exposures were comparable to those observed with the 25 mg dose of OBV.

Changes in DSV exposures ranged from 8% lower with duloxetine to 42% higher with ketoconazole. DSV doses of 300 mg BID to 800 mg BID have also been evaluated with peg-interferon plus ribavirin for 12 weeks [19,20]. DSV exposures across these doses ranged from 25% lower to 100% higher than those in the current studies and no changes in safety or efficacy were observed.

No dose adjustment is required for the DAAs based on the drug interactions discussed in this report. Carbamazepine and gemfibrozil are contraindicated with the OBV, PTV/r, and DSV regimen.

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 (Tables 3 and 4) and are discussed below.

*Mechanism-based drug interactions*

In the drug-drug interaction study with the potent CYP3A (and P-gp) inhibitor, ketoconazole, only minimal to modest increases in DAA or ritonavir exposures were observed. Though no dose adjustments for the DAAs are required, ketoconazole doses should be limited to 200 mg per day or less, as ketoconazole AUC values increased by 117%. The CYP2C8 inhibitor, gemfibrozil, significantly increased DSV exposures and coadministration of gemfibrozil and similar strong CYP2C8 inhibitors is contraindicated.

Carbamazepine, a CYP3A inducer, decreased PTV, ritonavir, and DSV exposures by 55% to 87%. Hence, carbamazepine and other strong CYP3A inducers are contraindicated with the 3D regimen of OBV, PTV/r, and DSV due to the potential for loss of antiviral efficacy.

Exposures of the CYP2C19 substrate, omeprazole, decreased when omeprazole was administered with the 3D regimen of OBV, PTV/r, and DSV, indicating the regimen had a mild inductive effect on CYP2C19. Though *a priori* dose modification is not required for omeprazole or other CYP2C19 substrates, higher doses should be considered if clinically indicated. Results from the study with the CYP2C9 substrate warfarin suggest that the 3D regimen does not induce or inhibit CYP2C9.

*In vitro* data suggest that PTV, ritonavir, and DSV are potential inhibitors of P-gp [12]. However, results from the study with digoxin suggest this is not the case *in vivo*.

*In vitro* data also indicate that PTV, ritonavir, and DSV are BCRP inhibitors, and that PTV is an OATP1B1/B3 inhibitor [12]. Accordingly, exposures of pravastatin (OATP1B1/B3 substrate) and rosuvastatin (OATP1B1/B3 plus BCRP substrate) showed



Please cite this article in press as: Menon RM et al. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.01.026

# Research Article

**Table 3. Dosing recommendations from mechanism-based drug-drug interactions.**

| Mechanism evaluated | Probe substrate, inhibitor, or inducer | Recommendation when coadministered with the 3D regimen |
|---|---|---|
| CYP2C8 and OATP1B1 inhibition | Gemfibrozil* | Strong CYP2C8 inhibitor, gemfibrozil, is contraindicated |
| CYP3A and P-gp inhibition | Ketoconazole | Limit ketoconazole and itraconazole doses to ≤200 mg per day. Lower doses are recommended for posaconazole |
| CYP3A and P-gp induction | Carbamazepine | Carbamazepine and other CYP3A inducers (e.g., phenytoin, phenobarbital, rifampin) are contraindicated |
| CYP2C9 inhibition | Warfarin | No dose adjustment required for warfarin. No interaction expected for other CYP2C9 substrates (e.g., NSAIDS 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 required; increase dose if clinically indicated for omeprazole and other CYP2C19 substrates (e.g., lansoprazole, esomeprazole, pantoprazole) |
| P-gp inhibition | Digoxin | No dose adjustment required for digoxin. No interaction expected for other P-gp substrates (e.g., talinolol) |
| OATP1B1/B3 and BCRP inhibition | Pravastatin | Reduce pravastatin dose by half / do not exceed 40 mg/day; lower doses recommended for other OATP1B1/B3 substrates (e.g., angiotensin II receptor blockers including valsartan, olmesartan, and telmisartan and statins including pitavastatin and fluvastatin) |
| | Rosuvastatin | Limit rosuvastatin dose to ≤10 mg per day; lower doses recommended for other BCRP substrates (e.g., sulfasalazine) |

*Evaluated with a PTV/r + DSV regimen only.

**Table 4. Dosing recommendations based on drug-drug interactions with commonly used medications.**

| Drug class | Medication | Recommendation when coadministered with the 3D regimen |
|---|---|---|
| Anti-addictives | 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 |
| Antihypertensives | Amlodipine | Reduce amlodipine dose by half. Decrease doses of other calcium channel blockers (e.g., nifedipine, verapamil, and diltiazem) with clinical monitoring. Avoid felodipine and nisoldipine |
| Anxiolytics/sleep aids | Zolpidem | No dose adjustment |
| | Alprazolam | No dose adjustment; clinical monitoring recommended |
| Diuretics | Furosemide | No dose adjustment; clinical monitoring recommended |
| Oral contraceptives | Norethindrone only | No dose adjustment |
| | Ethinyl estradiol containing* | Contraindicated |

*Ethinyl estradiol plus norgestimate interactions were evaluated with PTV/r, OBV ± DSV regimens.

clinically significant increases. Greater increases in rosuvastatin exposures (159% to 613%) compared to pravastatin exposures (37% to 82%) are likely due to the combined effect of OATP1B1/B3 plus BCRP inhibition for rosuvastatin compared with OATP1B1/B3 inhibition for pravastatin. Based on the magnitude of the interactions, the pravastatin dose should be reduced by half or limited to 40 mg and the rosuvastatin dose should be limited to ⩽10 mg per day when coadministered with the 3D regimen of OBV, PTV/r, and DSV.

*Interactions with other commonly used medications*

*Addiction treatment medications*

Patients receiving methadone or buprenorphine/naloxone do not require dose adjustments of these drugs when coadministered with the 3D regimen of OBV, PTV/r, and DSV. Although increases in exposures of buprenorphine and its metabolite, norbuprenorphine, were observed, these increases did not translate into pharmacodynamics changes.

*Antidepressants*

Exposures of escitalopram were minimally affected upon coadministration and no dose modification is needed. The 21% to 25% decreases in duloxetine exposures do not necessitate dose adjustment, as decreases in duloxetine exposures of up to 30% are not expected to affect efficacy [21].

*Antihypertensives*

Coadministration of the calcium channel blocker, amlodipine, with the 3D regimen of OBV, PTV/r, and DSV increased



Please cite this article in press as: Menon RM et al. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.01.026

amlodipine exposures by 26% to 157%, consistent with ritonavir-mediated inhibition of the metabolism of this CYP3A substrate. A 50% reduction in amlodipine dose is recommended when administered with the 3D regimen.

*Anxiolytic/sleep aid*
Zolpidem exposures were not affected by coadministration, but alprazolam AUC showed a modest 34% increase when alprazolam was coadministered with the 3D regimen of OBV, PTV/r, and DSV. No *a priori* dose adjustments are needed for alprazolam, although clinical monitoring is recommended.

*Diuretics*
Although the total exposure (AUC) of furosemide was minimally affected by coadministration with the 3D regimen of OBV, PTV/r, and DSV, peak exposure ($C_{max}$) increased by 42%. Based on this modest interaction and the well characterized safety profile of furosemide, no *a priori* dose adjustment is needed, but clinical monitoring is recommended.

*Oral contraceptives*
EE-containing products are contraindicated with the 3D regimen of OBV, PTV/r, and DSV due to ALT elevations. The mechanism for this pharmacodynamic interaction is not clear. The progestin-only contraceptive, norethindrone, can be administered with the 3D regimen.

*Conclusions*
A comprehensive evaluation of drug-drug interactions for the 3D regimen of OBV, PTV/r, and DSV and 20 medications was conducted in 13 separate studies. These investigations revealed that the majority of the commonly used medications can be coadministered with the 3D regimen without dose adjustment. Gemfibrozil and carbamazepine are contraindicated with the 3D regimen because they alter exposures of the DAAs. Concomitant administration of EE-containing contraceptives is contraindicated due to safety reasons though progestin-based oral contraceptives can be coadministered. Finally, no dose adjustment is necessary for the 3D regimen when coadministered with any of the evaluated medications that are not otherwise contraindicated.

## Conflict of interest

All authors are employees of AbbVie, Inc. and may hold stock or stock options.

## Financial support

The studies were sponsored by AbbVie. AbbVie contributed to the study design, research, and interpretation of data, and the writing, reviewing, and approving of the publication.

## Authors' contributions

Rajeev M. Menon contributed to study concept and design, analysis and interpretation of the data, and drafting of the manuscript. Prajakta S. Badri, Tianli Wang, Akshanth R. Polepally, Jiuhong Zha, and Amit Khatri, contributed to study concept and design, analysis and interpretation of the data, and review of the manuscript. Haoyu Wang and Beibei Hu contributed to statistical analysis and interpretation of data and review of the manuscript. Eoin P. Coakley and Thomas J. Podsadecki contributed to study concept and design, interpretation of the data, and revision of the manuscript for important intellectual content. Walid M. Awni contributed to study concept and design, interpretation of the data, and revision of the manuscript for important intellectual content. Sandeep Dutta contributed to study concept and design, statistical analysis, interpretation of the data, drafting of the manuscript, and revision of the manuscript for important intellectual content.

## Acknowledgements

We thank the study investigators, subjects, clinical sites, AbbVie personnel for their contribution to various aspects of the studies, and Allison Kitten (freelance writer under contract with AbbVie) for medical writing support.
The studies were sponsored by AbbVie. AbbVie contributed to the study design, research, and interpretation of data, and the writing, reviewing, and approving of the publication.

## References

[1] Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007;147:677–684.
[2] Bruno S, Crosignani A, Facciotto C, Rossi S, Roffi L, Redaelli A, et al. Sustained virologic response prevents the development of esophageal varices in compensated, Child-Pugh class A hepatitis C virus-induced cirrhosis. A 12-year prospective follow-up study. Hepatology 2010;51:2069–2076.
[3] Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. Clin Gastroenterol Hepatol 2011;9:923–930.
[4] Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011;9:509–516.
[5] Burger D, Back D, Buggisch P, Buti M, Craxí A, Foster G, et al. Clinical management of drug-drug interactions in HCV therapy: challenges and solutions. J Hepatol 2013;58:792–800.
[6] Serfaty L. Optimizing DAA management in daily practice. Dig Liver Dis 2013;45:S318–S322.
[7] Back D, Else L. The importance of drug-drug interactions in the DAA era. Dig Liver Dis 2013;45:S343–S348.
[8] Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014;370:1983–1992.
[9] Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1594–1603.
[10] Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370:1973–1982.
[11] Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014;147:359–365.
[12] Bow DAJ, Liu J, Kavetskaia O, Menon R, de Morais SM, Nijsen M, et al. A mechanistic non-clinical assessment of drug-drug interactions (metabolism and transporters) with the hepatitis C virus (HCV) regimen: ABT-450/r, ombitasvir and dasabuvir. In: Poster presented at: 2014 American Association for the Study of Liver Diseases/European Association for the Study of the Liver Special Conference on Hepatitis C; September 12–13, 2014; New York, NY.



Please cite this article in press as: Menon RM et al. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.01.026

# Research Article

[13] United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Draft Guidance; February 2012. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.

[14] European Medicines Agency. Guideline on the Investigation of Drug Interactions. CPMP/EWP/560/95/Rev. 1, 21 June 2012. Available from: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf>.

[15] Poordad F, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med 2013;368:45–53.

[16] Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med 2014;370:222–232.

[17] Mensing S, Polepally A, Konig D, Khatri A, Liu W, Podsadecki T, et al. Population pharmacokinetics of ABT-450, ombitasvir, dasabuvir, ritonavir and ribavirin in subjects with HCV genotype 1 infection [abstract T-007]. J Pharmacokinet Pharmacodyn 2014;41:S42.

[18] Sullivan GJ, Rodrigues-Torres M, Lawitz E, Poordad F, Kapoor M, Campbell A, et al. ABT-267 combined with pegylated interferon alpha-2a/ribavirin in genotype 1 (GT1) HCV-infected treatment-naive subjects: 12 week antiviral and safety analysis [abstract 1210]. J Hepatol 2012;56:S480.

[19] Gaultier IA, Cohen DE, Dumas EO, Larsen LM, Podsadecki TJ, Bernstein B. 12-Week efficacy and safety of ABT-072 or ABT-333 with pegylated interferon + ribavirin, following 3-day monotherapy in genotype 1 HCV-infected treatment-naïve subjects. In: Poster presented at: 21st Conference of the Asian Pacific Association for the Study of the Liver; February 17-20, 2011; Bangkok, Thailand. <http://www.natap.org/2011/APSL/APSL_02.htm>. Accessed October 17, 2014.

[20] Rodriguez-Torres M, Lawitz E, Cohen D, Larsen LM, Menon R, Collins C, et al. Treatment-naïve, HCV genotype 1-infected subjects show significantly greater HCV RNA decreases when treated with 28 days of ABT-333 plus peginterferon and ribavirin compared to peginterferon and ribavirin alone [abstract LB6]. In: Presented at: The 60th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2009; October 30-November 3; Boston, MA.

[21] Knadler MP, Lobo E, Chappell J, Bergstrom R. Duloxetine: clinical pharmacokinetics and drug interactions. Clin Pharmacokinet 2011;50:281–294.



Please cite this article in press as: Menon RM et al. Drug-drug interaction profile of the all-oral anti-hepatitis C virus regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.01.026