

Pharmacokinetics and safety of co-administered paritaprevir plus ritonavir, ombitasvir, and dasabuvir in hepatic impairment

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Background & Aims: Paritaprevir, ombitasvir, and dasabuvir are direct-acting antivirals for treatment of chronic hepatitis C virus (HCV) infection. The aim of this study was to characterize the effects of mild, moderate, and severe hepatic impairment on the pharmacokinetics of these drugs.

Methods: HCV-negative subjects with normal hepatic function (n = 7) or mild (Child-Pugh A, n = 6), moderate (Child-Pugh B, n = 6), or severe (Child-Pugh C, n = 5) hepatic impairment received a single-dose of the combination of paritaprevir plus ritonavir (paritaprevir/r, 200/100 mg), ombitasvir (25 mg), and dasabuvir (400 mg). Plasma samples were collected through 144 hours after administration for pharmacokinetic assessments.

Results: Paritaprevir, ombitasvir, dasabuvir, and ritonavir exposures (maximal plasma concentration, C_{max} , and area under the concentration-time curve, AUC) were minimally affected in subjects with mild or moderate hepatic impairment. Differences in exposures between healthy controls and subjects with mild or moderate hepatic impairment were less than 35%, except for 62% higher paritaprevir AUC in subjects with moderate hepatic impairment. Paritaprevir and dasabuvir AUC were significantly higher in subjects with severe hepatic impairment (950% and

325%, respectively). However, ombitasvir AUC was 54% lower and ritonavir AUC was comparable. Adverse events included eye stye, insomnia, and pain from an infiltrated intravenous line. **Conclusions:** The changes observed in paritaprevir, ritonavir, ombitasvir, and dasabuvir exposures in subjects with mild or moderate hepatic impairment do not necessitate dose adjustment. Subjects with severe hepatic impairment had substantially higher paritaprevir and dasabuvir exposures.

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Introduction

Chronic hepatitis C virus (HCV) infection is a leading cause of liver disease worldwide. Each year, three to four million new HCV infections are anticipated and approximately 350,000 people will die of complications associated with HCV [1]. HCV-induced inflammation may cause progressive liver fibrosis, which results in cirrhosis, hepatocellular carcinoma, end-stage liver disease, and eventually transplant or death [2,3]. Because HCV infection results in hepatic impairment in a large number of patients, characterization of the effects of hepatic impairment on the pharmacokinetics of HCV treatments is essential.

Paritaprevir (ABT-450), ombitasvir (ABT-267), and dasabuvir (ABT-333) are direct-acting antiviral agents (DAAs) approved for interferon-free combination treatment of chronic HCV infection. Paritaprevir is a nonstructural (NS) protein 3/4A protease inhibitor identified by AbbVie and Enanta as a lead compound for clinical development. Paritaprevir is metabolized primarily by cytochrome P450 (CYP) 3A and is given with a low dose of ritonavir, a potent CYP3A inhibitor, as a pharmacokinetic enhancer to enable once daily dosing at a lower dose of paritaprevir (co-administration denoted paritaprevir/r). Ombitasvir is a NS5A inhibitor and dasabuvir is a non-nucleoside NS5B polymerase inhibitor. Combination treatment of HCV genotype (GT) 1-infected patients with these three DAAs (ombitasvir/paritaprevir/ritonavir and dasabuvir) plus ribavirin for 12 weeks results in sustained virologic responses 12 weeks (SVR₁₂) after the end of treatment in 92% of patients with compensated cirrhosis (96% for 24 weeks of treatment) and 96% to 99.5% of patients without cirrhosis [4,5]. Hepatic elimination, metabolism, and

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Abbreviations: HCV, hepatitis C virus; C_{max} , maximal plasma concentration; AUC, area under the plasma concentration-time curve; DAA, direct-acting antiviral agent; NS, nonstructural; CYP, cytochrome P450; Paritaprevir/r, paritaprevir administered with ritonavir; SVR₁₂, sustained virologic response 12 weeks post-treatment; BMI, body mass index; ECG, electrocardiogram; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; OATP, organic anion transporting polypeptide; LLOQ, lower limit of quantitation; CV, coefficient of variation; T_{max} , time to maximum observed plasma concentration (C_{max}); β , apparent terminal phase elimination rate constant; $t_{1/2}$, terminal phase elimination half-life; CL/F, apparent oral clearance; $V_{d/F}$, apparent volume of distribution; f_u , unbound fraction; ANCOVA, analysis of covariance; CI, confidence interval; GT1, genotype 1; P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; SD, standard deviation.



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biliary excretion of parent drug and metabolites are the primary routes of elimination of paritaprevir, ombitasvir, and dasabuvir. In humans, following administration of a single-dose of 200 mg [¹⁴C]-paritaprevir with 100 mg ritonavir or 600 mg [¹⁴C]-ritonavir or 25 mg [¹⁴C]-ombitasvir or 400 mg [¹⁴C]-dasabuvir, approximately 86.4% to 94.4% and 1.9% to 11.3% of the radioactive doses of the DAAs and ritonavir were eliminated in feces and urine, respectively [AbbVie, unpublished data].

Chronic liver disease can significantly affect hepatic drug metabolism and elimination, thus potentially affecting the pharmacokinetics of drugs that are primarily eliminated by the liver. Because the liver is the primary site for elimination and the pharmacodynamic activity of DAAs, this study was conducted to characterize the effects of varying degrees of hepatic impairment on DAA and ritonavir pharmacokinetics to inform dosing recommendations for HCV-infected patients with mild, moderate, or severe hepatic impairment based on Child-Pugh scores.

Study design and methods

Study design and study population

The study was conducted at three sites (Orlando Clinical Research Center, Orlando, Florida, USA; Texas Liver Institute, San Antonio, Texas, USA; and Indiana University Health University Hospital, Indianapolis, Indiana, USA) in accordance with Good Clinical Practice guidelines and ethical principles that have their origin in the Declaration of Helsinki. The protocol was approved by the institutional review boards (Quorum Review, Inc., Seattle, WA and Indiana University Office of Research Administration, Indianapolis, IN) and written informed consent was obtained from each subject before any study-related procedures were performed.

The study was an open-label, multicenter, single-dose, two-part study in subjects with normal hepatic function ($n = 7$) and subjects with mild ($n = 6$), moderate ($n = 6$), or severe ($n = 5$) hepatic impairment. Eligible subjects were non-Asian males and females between the ages of 18 and 65 years, inclusive, who had a body mass index (BMI) of 18 to 37 kg/m², inclusive. To ensure a more homogeneous study population, Asian subjects were not enrolled because of potentially higher paritaprevir exposures in persons of Asian descent [6]. Subjects with normal hepatic function were in general good health based on medical history, physical examination, laboratory tests, and 12-lead electrocardiograms (ECGs) and had negative test results for hepatitis B surface antigen and HCV antibody. Subjects with hepatic impairment were in a stable condition, had Child-Pugh classification categories of A (mild), B (moderate), or C (severe) based on Child-Pugh scores of 5 to 6, 7 to 9, and 10 to 12, respectively [7–9], and had clinically significant liver disease other than chronic HCV infection diagnosed by liver biopsy or imaging techniques or had a medical history of chronic liver disease. Additional criteria considered for the presence of clinically significant hepatic impairment included: positive test results for hepatitis B; history of alcoholic liver disease; diagnosis of hepatomegaly, ascites, palmar erythema, spider angioma, abdominal venous collaterals, testicular atrophy and excluding non-hepatic causes of hepatomegaly; elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than the upper limit of normal (ULN) reference range but below 6× the ULN reference range; and alkaline phosphatase, total bilirubin, or prolonged prothrombin time elevation greater than the ULN reference range or an albumin value below the lower limit of the laboratory reference range.

Major exclusion criteria for all subjects included positive test results for human immunodeficiency virus antibody, history of drug sensitivity, use of medications contraindicated with ritonavir or known inhibitors or inducers of CYP3A, CYP2C8, organic anion transporting polypeptide (OATP) 1B1, or OATP1B3 taken within one month prior to study drug administration. Subjects could not be enrolled if they were female and were pregnant or breastfeeding.

In Part 1 of the study, subjects with mild hepatic impairment and those with normal hepatic function who were demographically matched based on age (± 5 years), weight (± 5 kg), sex, current smoking status (smokers or non-smokers), race, and ethnicity were enrolled. In Part 2 of the study, subjects with moderate or severe hepatic impairment were sequentially enrolled after review of data from Part 1. All subjects received a single-dose of paritaprevir/r 200 mg/100 mg, ombitasvir 25 mg, and dasabuvir 400 mg administered in the morning of

study day one under non-fasting conditions following administration of breakfast (335 kcal, with approximately 21%, 67%, and 12% of kcal from fat, carbohydrates, and protein, respectively). Subjects were confined to the study site beginning on study day one and ending after collection of the last blood sample and completion of study procedures on study day five. Subjects received appropriate standardized diets throughout the study.

Sample collection and bioanalytical methods

Blood samples for determination of paritaprevir, ritonavir, ombitasvir, dasabuvir, and dasabuvir M1 metabolite concentrations were obtained by venipuncture prior to dosing (0 hour) and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 72, 96, and 144 hours after dosing. Samples for determination of protein binding were collected prior to dosing (0 hour). Blood samples were collected into ethylenediaminetetraacetic acid tubes and stored on ice until centrifugation and plasma samples were stored at -20°C until analysis.

Plasma concentrations of paritaprevir and ritonavir were determined using a validated 96-well salting-out assisted liquid/liquid extraction high performance liquid chromatography method with tandem mass spectrometric detection. The lower limits of quantitation (LLOQs) for paritaprevir and ritonavir were 0.492 ng/ml and 4.97 ng/ml, respectively. The coefficients of variation (CVs) were $\leq 9.4\%$ and $\leq 8.3\%$, respectively. Plasma concentrations of ombitasvir were determined using a validated 96-well liquid-liquid extraction high performance liquid chromatography method with tandem mass spectrometric detection. The LLOQ for ombitasvir was 0.126 ng/ml and the CV was $\leq 5.5\%$. Plasma concentrations of dasabuvir and dasabuvir M1 were determined using a validated 96-well on-line solid-phase extraction high performance liquid chromatography method with tandem mass spectrometric detection. The LLOQs for dasabuvir and dasabuvir M1 were 1.01 ng/ml and 2.07 ng/ml, respectively, and the CVs were $\leq 5.5\%$ and $\leq 14.9\%$, respectively. For all assays, samples for each subject were analyzed in the same analytical run.

Pharmacokinetic evaluations

Non-compartmental methods were used to evaluate the following values for paritaprevir, ritonavir, ombitasvir, dasabuvir, and dasabuvir M1: maximum observed plasma concentration (C_{max}) and time to C_{max} (T_{max}), apparent terminal phase elimination rate constant (β), half-life ($t_{1/2}$), area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration (AUC_t) and to infinite time (AUC_{∞}), apparent oral clearance (CL/F), apparent volume of distribution (V_{β}/F), and unbound fraction (f_u).

Safety and tolerability

Safety and tolerability were evaluated based on adverse event monitoring, vital signs measurements, physical examinations, 12-lead ECG assessments, and laboratory tests.

Statistical analysis

All statistical tests were two-tailed and were performed at significance level of 0.05. Computation for the statistical tests was performed with SAS, Version 9.2 (Cary, NC). For the linear mixed effects model analysis, SAS procedure MIXED was used with Kenward-Roger option specified. SAS procedure PROC UNIVARIATE and PROC MEANS were used to obtain summary statistics.

An analysis of covariance (ANCOVA) was performed on AUC , C_{max} , CL/F , and V_{β}/F based on total concentrations, as well as T_{max} and β . ANCOVA was also performed for unbound AUC , C_{max} , CL_{u}/F , $V_{\beta\text{u}}/F$, and f_u . For AUC , C_{max} , CL/F , and V_{β}/F (based on both total and unbound concentrations), the logarithmic transformation was used. For f_u , logit transformation was used. Hepatic function category was the primary factor of interest. Body weight and age were considered as possible covariates; however, age was not statistically significant at the 0.10 level and was not included in the final model. Sex was not included because there were no female subjects with moderate or severe hepatic impairment. Within the framework of the ANCOVA, the effect of each hepatic impairment level was estimated and compared to the normal category at a significance level of 0.05. For AUC and C_{max} , the point estimates of the central value ratios and their 90% confidence intervals (CIs) were provided for each hepatic impairment group with respect to the normal group. These point estimates and the 90% CIs for the central value ratios were obtained by taking the anti-logarithm of the differences in the least squares means on the logarithmic scale, as well as the upper and lower limits of the 90% CIs for the differences within the framework of ANCOVA.

Linear regression analyses were also performed using total and unbound AUC_{∞} and CL/F , $t_{1/2}$, and $V_{d/F}$ as dependent variables, and Child-Pugh score, serum albumin concentrations, and international normalized ratio as the independent predictors. Separate analyses were conducted for each pair of dependent and independent variables for each drug. Age and weight were included as covariates.

Results

Baseline demographics

Subjects with mild hepatic impairment were well matched to subjects with normal hepatic function with regard to age, weight, BMI, sex, smoking status and race/ethnicity, as specified in the protocol (Table 1). Subjects with moderate or severe hepatic impairment, all of whom were male, were also similar to those with normal hepatic function except that most had a history of being drinkers or ex-drinkers of alcohol.

Pharmacokinetics in mild and moderate hepatic impairment

The mean plasma concentration vs. time profiles for the DAAs and ritonavir over 144 hours following single-dose administration of paritaprevir/r, ombitasvir, and dasabuvir in subjects with normal hepatic function and those with hepatic impairment are shown in Fig. 1. Pharmacokinetic parameters for paritaprevir, ombitasvir, dasabuvir, dasabuvir M1, and ritonavir are presented in Table 2 and the central value ratios and 90% CIs for C_{max} and AUC by hepatic function category (mild, moderate, or severe impairment) are presented in Fig. 2.

Mild and moderate hepatic impairment had a minimal to moderate impact on the single-dose pharmacokinetics of paritaprevir, ombitasvir, dasabuvir, dasabuvir M1, and ritonavir. The differences in C_{max} and AUC values of the DAAs and ritonavir

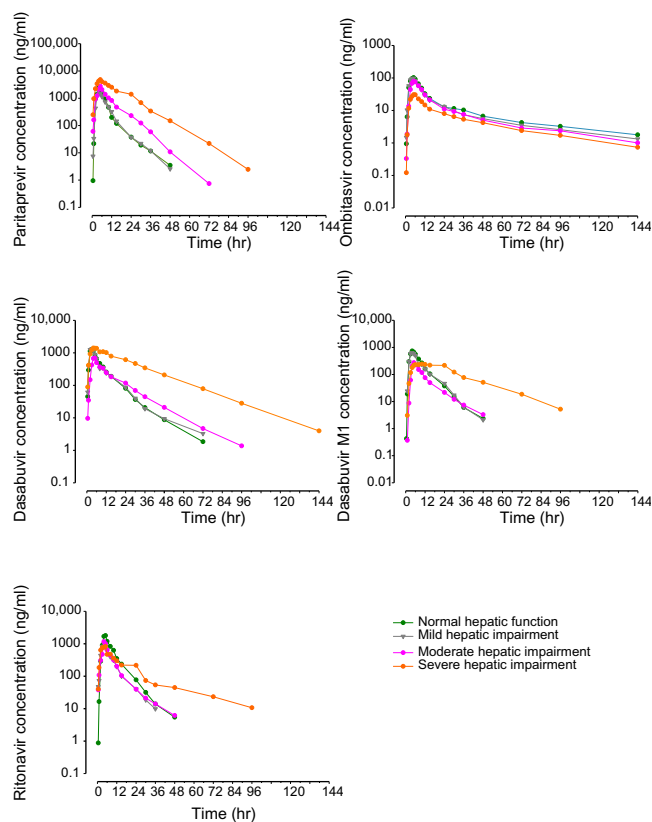


Fig. 1. Mean plasma concentration vs. time profiles (log-linear scale) of the DAAs and ritonavir in subjects with normal hepatic function and those with mild, moderate, or severe hepatic impairment.

Table 1. Demographics and baseline characteristics.

Variable	Normal hepatic function N = 7	Mild hepatic impairment N = 6	Moderate hepatic impairment N = 6	Severe hepatic impairment N = 5
Age (yr), median (range)	52 (47-57)	51.5 (49-64)	56 (46-60)	48 (40-62)
Weight (kg), median (range)	94.0 (61-108)	87.5 (64-109)	80.5 (63-103)	94.0 (70-107)
Body mass index (kg/m ²), median (range)	33.0 (23.5-35.7)	27.5 (23.4-34.0)	24.9 (20.8-34.5)	31.4 (23.4-36.1)
Sex, n (%)				
Female	3 (42.9)	3 (50)	0	0
Male	4 (57.1)	3 (50)	6 (100)	5 (100)
Race, n (%)				
White	6 (85.7)	5 (83.3)	6 (100)	4 (80.0)
Black	1 (14.3)	0	0	1 (20.0)
Other	0	1 (16.7)	0	0
Tobacco, n (%)				
User	3 (42.9)	2 (33.3)	3 (50)	3 (60)
Ex-user*	0	3 (50)	0	0
Non-user	4 (57.1)	1 (16.7)	3 (50)	2 (40)
Alcohol, n (%)				
Drinker	1 (14.3)	1 (16.7)	3 (50)	0
Ex-drinker	1 (14.3)	4 (66.7)	3 (50)	4 (80)
Non-drinker	5 (71.4)	1 (16.7)	0	1 (20)

*Ex-users were considered non-users for matching enrollment criteria and data analyses.

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Table 2. Single-dose pharmacokinetic parameters of the DAAs and ritonavir in subjects with normal hepatic function and those with hepatic impairment.

Parameter	Paritaprevir			
	Normal (N = 7)	Mild (N = 6)	Moderate (N = 6)	Severe (N = 5)
C_{max} (ng/ml)*	1340 (111)	713 (130)	2220 (75)	5310 (35)
T_{max} (hr) [†]	4.0 (4.0-5.0)	4.0 (2.0-10.0)	4.5 (2.0-5.0)	5.0 (4.0-10.0)
AUC_{∞} (ng*hr/ml)*	6990 (124)	5060 (142)	14,300 (106)	68,800 (40)
$t_{1/2}$ (hr) [‡]	5.8 (1.6)	5.9 (1.9)	6.4 (0.7)	7.9 (1.3)
CL/F (L/hr) [§]	49 (49)	75 (79)	23 (26)	3.1 (1.1)
f_u (%) [§]	1.1 (0.3)	0.78 (0.1)	0.75 (0.1)	1.2 (0.2)
Ombitasvir				
C_{max} (ng/ml)*	101 (42)	102 (24)	78 (37)	31 (35)
T_{max} (hr) [†]	4.0 (3.0-6.0)	4.5 (3.0-5.0)	5.0 (4.0-6.0)	5.0 (3.0-6.0)
AUC_{∞} (ng*hr/ml)*	1540 (51)	1430 (37)	1200 (42)	683 (41)
$t_{1/2}$ (hr) [‡]	55 (15)	47 (9.9)	43 (17)	45 (6.4)
CL/F (L/hr) [§]	18 (8.3)	18 (5.3)	22 (8.9)	40 (18)
f_u (%) [§]	0.021 (0.005)	0.023 (0.008)	0.020 (0.007)	0.047 (0.011)
Dasabuvir				
C_{max} (ng/ml)*	1070 (88)	1340 (37)	723 (25)	1390 (46)
T_{max} (hr) [†]	4.0 (2.0-5.0)	2.5 (2.0-4.0)	4.0 (4.0-5.0)	4.0 (3.0-6.0)
AUC_{∞} (ng*hr/ml)*	8060 (82)	9550 (46)	7580 (39)	33,200 (43)
$t_{1/2}$ (hr) [‡]	9.2 (4.1)	8.3 (4.5)	11 (4.0)	17 (1.4)
CL/F (L/hr) [§]	63 (47)	45 (15)	57 (27)	14 (8.0)
f_u (%) [§]	0.61 (0.29)	0.29 (0.09)	0.28 (0.05)	0.42 (0.12)
Dasabuvir M1				
C_{max} (ng/ml)*	656 (70)	592 (48)	229 (61)	252 (57)
T_{max} (hr) [†]	4.0 (4.0-5.0)	3.5 (3.0-5.0)	5.0 (5.0-8.0)	10.0 (4.0-24.0)
AUC_{∞} (ng*hr/ml)*	4300 (93)	4390 (72)	2150 (48)	7310 (54)
$t_{1/2}$ (hr) [‡]	5.2 (1.0)	5.4 (1.9)	7.6 (2.8)	16 (2.2)
CL/F (L/hr) [§]	117 (67)	109 (66)	200 (77)	65 (46)
f_u (%) [§]	5.8 (0.81)	5.1 (1.0)	5.4 (0.59)	6.8 (1.7)
Ritonavir				
C_{max} (ng/ml)*	1580 (67)	950 (55)	1190 (30)	990 (54)
T_{max} (hr) [†]	4.0 (4.0-5.0)	4.0 (3.0-10.0)	4.0 (3.0-5.0)	4.0 (2.0-10.0)
AUC_{∞} (ng*hr/ml)*	9750 (63)	6430 (44)	6820 (39)	11,000 (56)
$t_{1/2}$ (hr) [‡]	5.2 (1.4)	5.4 (1.5)	6.7 (1.7)	18 (16)
CL/F (L/hr) [§]	15 (16)	18 (13)	16 (7.4)	9.9 (4.0)
f_u (%) [§]	0.63 (0.16)	0.52 (0.23)	0.60 (0.25)	0.69 (0.18)

*Geometric mean (CV%).

[†]Median (range).[‡]Harmonic mean (pseudo-SD).[§]Mean (SD).

among subjects with normal hepatic function and those with mild hepatic impairment were less than 35%, except for the 40% and 48% lower C_{max} values for ritonavir and paritaprevir, respectively. The differences in C_{max} and AUC values of the DAAs and ritonavir among subjects with normal hepatic function and those with moderate hepatic impairment were less than 40%, except for the 62% higher paritaprevir AUC values and 57% to 68% lower dasabuvir M1 C_{max} and AUC values. Paritaprevir, ombitasvir, dasabuvir, dasabuvir M1, and ritonavir T_{max} and $t_{1/2}$ were comparable between subjects with normal hepatic function and those with mild or moderate hepatic impairment (Table 2).

Pharmacokinetics in severe hepatic impairment

Severe hepatic impairment had a substantial impact on the single-dose pharmacokinetics of paritaprevir and dasabuvir.

Paritaprevir C_{max} and AUC values were 325% (central value ratio: 4.25) and 950% (central value ratio: 10.5) higher, respectively, and dasabuvir C_{max} and AUC values were 34% (central value ratio: 1.34) and 325% (central value ratio: 4.25) higher, respectively, in subjects with severe hepatic impairment compared to subjects with normal hepatic function (Fig. 2). Ombitasvir, ritonavir, and dasabuvir M1 exposures were affected to a lesser extent. Ombitasvir C_{max} and AUC values were 68% and 54% lower, respectively, ritonavir C_{max} and AUC values were 35% lower and 13% higher, respectively, and dasabuvir M1 C_{max} and AUC values were 60% lower and 77% higher, respectively, in subjects with severe hepatic impairment compared to those with normal hepatic function.

Paritaprevir and ombitasvir T_{max} and $t_{1/2}$ and ritonavir and dasabuvir T_{max} were comparable between subjects with severe hepatic impairment and those with normal hepatic function;

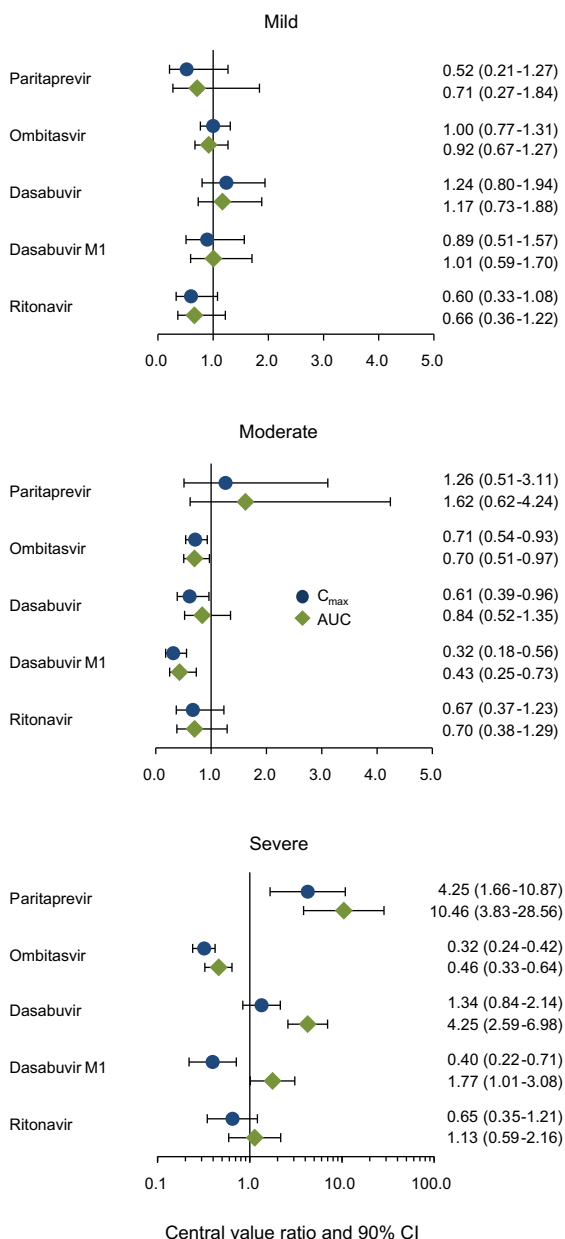


Fig. 2. Central value ratios and their 90% CIs for DAA and ritonavir C_{max} and AUC in subjects with hepatic impairment compared to those with normal hepatic function. Point estimates represent the central value ratios. CI, confidence interval. Note: severe hepatic impairment is shown on a logarithmic scale. (This figure appears in colour on the web.)

however, dasabuvir $t_{1/2}$ was approximately seven hours longer (17 ± 1.4 vs. 9.2 ± 4.1 hours) and ritonavir $t_{1/2}$ was approximately 12 hours longer (18 ± 16 vs. 5.2 ± 1.4 hours). Dasabuvir M1 T_{max} and $t_{1/2}$ were approximately six and 11 hours longer, respectively, in subjects with severe hepatic impairment (Table 2). The results based on regression analyses generally agreed with results based on ANCOVA analyses (data not shown).

Plasma protein binding

The plasma unbound fractions of the DAAs and ritonavir were comparable in subjects with hepatic impairment and those with

normal hepatic function and the values had no rank order across the severity of hepatic impairment (Table 2). The only exception was the plasma unbound fraction of ombitasvir in subjects with severe hepatic impairment, which was approximately two-fold higher compared to that in subjects with normal hepatic function. All of the DAAs and ritonavir are highly protein bound. The percent unbound was approximately 1% or less for paritaprevir, dasabuvir, ombitasvir, and ritonavir and approximately 6% for dasabuvir M1. The small magnitude of differences and a lack of trend across the severity of hepatic impairment suggest the differences among the hepatic function groups may be due to assay limitations.

Based on statistical analysis (ANCOVA) of unbound C_{max} and AUC for the DAAs and ritonavir, the effects of hepatic impairment on these unbound pharmacokinetic parameters were generally similar to the effects of hepatic impairment on total pharmacokinetic parameters (data not shown).

Safety

Two subjects experienced adverse events during the study. One subject with mild hepatic impairment experienced a left eye hordeolum (stye), and one subject with severe hepatic impairment experienced insomnia, which had an onset before the first dose of study drug, and infusion site pain from an infiltrated intravenous line. These events were mild in severity, did not lead to discontinuation from the study, and were considered not related or probably not related to the study drugs. No clinically significant vital signs changes, ECG parameters, or laboratory measurements were observed.

Discussion

This study was designed to characterize the effects of mild, moderate and severe hepatic impairment on the pharmacokinetics of paritaprevir, ombitasvir, dasabuvir, and ritonavir to inform dosing recommendations for these DAAs and ritonavir in HCV-infected patients with hepatic impairment. Differences in DAA and ritonavir exposures (AUC) between subjects with normal hepatic function and those with mild or moderate hepatic impairment were less than 35% and were generally similar, based on total and unbound concentrations, except for 62% higher paritaprevir AUC values in subjects with moderate hepatic impairment. DAA and ritonavir T_{max} and $t_{1/2}$ were not affected by mild or moderate hepatic impairment. The major metabolite of dasabuvir, dasabuvir M1, possesses a small but significant amount of antiviral activity. Similar to the DAAs and ritonavir, dasabuvir M1 exposures, T_{max} , and $t_{1/2}$ were not substantially altered in subjects with mild or moderate hepatic impairment. Taken together, data from the current study suggest that the approved clinical doses of paritaprevir/r (150/100 mg once daily), ombitasvir (25 mg once daily), and dasabuvir (250 mg twice daily) can be safely administered with no dose adjustment in HCV-infected patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. This conclusion is supported by safety and efficacy data from Phase II clinical trials of the 3-DAA combination regimen of paritaprevir/r, ombitasvir, and dasabuvir, with or without ribavirin, in HCV-infected subjects without hepatic impairment (non-cirrhotic subjects) [10–12]. In these Phase II studies, higher paritaprevir/r doses up to

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250/100 mg once daily for 12 to 24 weeks in combination with other DAAs, with or without ribavirin, ombitasvir doses up to 200 mg once daily, or dasabuvir doses up to 800 mg twice daily for 12 weeks in combination with pegylated interferon/ribavirin were administered to HCV GT1-infected subjects. The safety profile of the DAAs was similar to that observed in the Phase III studies even though the DAA exposures at these higher doses in the Phase II studies were expected to provide at least twofold higher exposures than the Phase III doses.

The pharmacokinetics of paritaprevir and dasabuvir were substantially altered in subjects with severe hepatic impairment (Child-Pugh C) such that AUC values based on total concentrations were 10.5-fold and 4.25-fold, respectively, of those in subjects with normal hepatic function. Dasabuvir also had a longer $t_{1/2}$ (16.7 vs. 9.2 hours), as did ritonavir (18.3 vs. 5.17 hours). Dasabuvir M1 exposures were minimally affected by severe hepatic impairment, but dasabuvir M1 T_{max} and $t_{1/2}$ were 6 and 11 hours longer, respectively. In contrast, changes in ombitasvir and ritonavir exposures were modest and are not expected to be clinically relevant. As a result of significantly higher paritaprevir and dasabuvir exposures, the 3-DAA combination of ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily, and dasabuvir 250 mg twice daily is currently not recommended for HCV-infected subjects with severe hepatic impairment (Child-Pugh C).

In this study, ombitasvir exposures were lower in subjects with severe hepatic impairment. Ombitasvir is a substrate of efflux transporters, such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and is primarily eliminated via the biliary route. These efflux transporters are present on the canalicular side of hepatocytes and facilitate biliary excretion of their substrates. Upregulation of P-gp efflux transporters as an adaptive mechanism to limit the accumulation of toxic biliary constituents has been observed in liver samples from patients with advanced primary biliary cirrhosis [13]. Higher BCRP mRNA and protein expression has also been observed in liver tissue from subjects with alcoholic or diabetic cirrhosis [14]. The upregulation of these efflux transporters could explain the decrease in ombitasvir exposures in subjects with hepatic impairment in this study. Similar decreases in exposures have been observed for other NS5A inhibitors, such as daclatasvir and GS-5816, in subjects with hepatic impairment [15,16]. Daclatasvir and GS-5816 are both substrates of P-gp transporters and GS-5816 is also an inhibitor of P-gp [17,18].

Paritaprevir exposures were slightly higher in subjects with moderate hepatic impairment and substantially higher in subjects with severe hepatic impairment. Paritaprevir is a substrate and inhibitor of OATP1B1 and OATP1B3 and is eliminated primarily through the hepatic route. These transporters are predominately located in the sinusoidal membrane of hepatocytes, where they extract substrates from blood into hepatocytes. Downregulation of OATP1B1 protein levels and OATP1B1 and OATP1B3 mRNA expression has been observed in liver samples from patients with advanced primary biliary cirrhosis or alcoholic cirrhosis [13,14]. Increased exposures of other NS3/4A protease inhibitors, such as asunaprevir and simeprevir, have been observed in subjects with moderate or severe hepatic impairment. In subjects with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment, asunaprevir C_{max} and AUC were 5.03- and 9.83-fold, respectively, and 22.92- and 32.08-fold, respectively, of the values in subjects with normal

hepatic function [19]. Similarly, in subjects with moderate hepatic impairment (Child-Pugh B), simeprevir C_{max} and AUC were 1.76-fold and 2.62-fold of the values, respectively, in subjects with normal hepatic function [20]. Asunaprevir and simeprevir are both hepatically eliminated, primarily via OATP1B1/2B1 and OATP1B1/3, respectively [21,22]. Although not measured in the current study, reduced expression of these uptake transporters in subjects with moderate or severe hepatic impairment could result in reduced paritaprevir uptake, reduced clearance, and higher plasma exposures.

Paritaprevir shows non-linear pharmacokinetics with a greater than dose-proportional increase in exposure with increase in dose. Reduced presystemic metabolism due to intra- and extra-hepatic portal-systemic shunting, which may reduce the first-pass effect and increase paritaprevir absorption in the gut, may also cause increased paritaprevir exposures in subjects with hepatic impairment. Also, the subjects in the control group (normal hepatic function) were not matched to subjects with moderate or severe hepatic impairment, which combined with the higher paritaprevir between-subject variability, could have resulted in differences in paritaprevir exposures between these groups.

The variability in paritaprevir exposure was lower in subjects with severe hepatic impairment compared to the other subjects in this study or healthy subjects in other Phase I studies [AbbVie, unpublished data]. Human liver microsomes from patients with cirrhosis or cirrhosis and cholestasis have been shown to have approximately 25% to 90% lower expression of CYP3A4 activity [23]. CYP3A protein concentrations and enzymatic activity were also lower in patients with non-cholestatic liver cirrhosis [24,25]. The reduced variability in paritaprevir exposure in subjects with severe hepatic impairment could be due to lower baseline CYP3A activity, which could be more effectively (or completely) blocked by ritonavir.

Dasabuvir C_{max} was comparable, but AUC was higher and $t_{1/2}$ was seven hours longer in subjects with severe hepatic impairment compared to subjects with normal hepatic function. These results suggest that reduced hepatic metabolism and biliary elimination rather than increased absorption or a reduced first-pass effect may cause increased dasabuvir exposures in these subjects.

The effects of hepatic impairment on dasabuvir M1 metabolite pharmacokinetics were variable. Dasabuvir M1 C_{max} and AUC were unaffected by mild hepatic impairment, decreased by moderate hepatic impairment, and both decreased (C_{max}) and increased (AUC) by severe hepatic impairment. The pharmacokinetic profile of the dasabuvir M1 metabolite closely follows that of the parent drug, which has formation-rate limited pharmacokinetics. Dasabuvir M1 T_{max} and $t_{1/2}$ were six and 11 hours longer, respectively, in subjects with severe hepatic impairment. The increase in dasabuvir M1 $t_{1/2}$ in subjects with severe hepatic impairment closely follows that of dasabuvir in these subjects. Dasabuvir M1 metabolite gets further metabolized before being eliminated. The increase in dasabuvir M1 $t_{1/2}$ and AUC could be due to reduced dasabuvir metabolism and hepatic uptake, resulting in a reduced rate of formation and elimination of dasabuvir M1, reduced dasabuvir M1 metabolism, or a combination of both.

Ritonavir C_{max} values were 35% to 40% lower in subjects with hepatic impairment, regardless of severity, compared with subject with normal hepatic function. Ritonavir AUC values were also lower, except in severe hepatic impairment, in which the AUC value was slightly higher. Ritonavir $t_{1/2}$ was also longer in

subjects with severe hepatic impairment. *In vitro* studies using human liver microsomes have shown that CYP3A and CYP2D6 are involved in ritonavir metabolism [26]. As noted previously, a decrease in CYP3A protein content and activity has been observed in patients with liver disease. A reduction in CYP2D6 activity by approximately 70% has also been observed in patients with decompensated liver disease [27]. The increase in ritonavir $t_{1/2}$ and AUC in subjects with severe hepatic impairment could be due to a reduction in ritonavir metabolism, resulting in a reduction in ritonavir clearance.

The formulations of paritaprevir, ritonavir, ombitasvir, and dasabuvir used in the current study are different from the marketed formulations used in the Phase III studies. However, because the exposures of the marketed formulations in healthy volunteers have been shown in other studies to be comparable to, or in the case of paritaprevir, approximately 30% lower than, the exposures from the doses and formulations of the DAAs used in the current study, the effects of hepatic impairment on the marketed formulations are expected to be similar.

The pharmacokinetic results from this study and the safety and efficacy data from Phase II studies in HCV-infected patients with normal liver function were used to support administration of the 3-DAA regimen of ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily and dasabuvir 250 mg twice daily to treatment-naïve and pegylated interferon/ribavirin treatment-experienced HCV GT1-infected subjects with compensated cirrhosis (Child-Pugh A) for 12 or 24 weeks; the efficacy (SVR₁₂ rates of 92% to 96%, respectively) and safety of the 3-DAA combination regimen in these patients was comparable to that observed in HCV patients without cirrhosis in other Phase III studies [5]. Based on these results, the safety, efficacy, and pharmacokinetics of the 3-DAA regimen are being evaluated in subjects with decompensated cirrhosis (Child-Pugh B) in an ongoing study (NCT02219477).

Although the single-dose administration and small sample size of six to seven subjects per group are potential limitations of our study, this type of study design is widely used to understand the effect of hepatic impairment on the pharmacokinetics of drugs and to provide dosing recommendations in the presence of hepatic impairment. Enrolling a larger cohort of subjects, especially those with moderate or severe hepatic impairment, for multiple-dose administration is extremely challenging due to the lack of any potential benefits for the study participants.

The single-dose pharmacokinetic results from this study in subjects with mild or moderate hepatic impairment can potentially be extrapolated to steady-state conditions. This is primarily because no accumulation of ombitasvir or dasabuvir was observed following administration of the 3-DAA regimen in Phase I studies and mild or moderate hepatic impairment did not affect the half-lives of the DAAs. Hence, the single-dose pharmacokinetic results for these drugs are reflective of those at steady state. Paritaprevir shows 1.5- to 2-fold accumulation following multiple dosing, which is primarily driven by ritonavir. Because ritonavir exposures in subjects with mild or moderate hepatic impairment were approximately 30% to 40% lower than those in subjects with normal hepatic function, the extent of paritaprevir accumulation at steady state could be lower in subjects with hepatic impairment, partially offsetting the 62% increase in paritaprevir exposures observed in subjects with

moderate hepatic impairment following single-dose administration. Additionally, pharmacokinetic, safety, and efficacy data from an ongoing study of the 3-DAA regimen in subjects with decompensated cirrhosis (Child-Pugh B) (NCT02219477) will be used to provide dosing recommendations for the 3-DAA regimen in this patient population. Extrapolation of DAA exposures to steady state in subjects with severe hepatic impairment is difficult, especially for paritaprevir and dasabuvir, due to the extent of the increase in their exposures.

In conclusion, pharmacokinetic data from the present study suggest that HCV-infected patients with mild (Child-Pugh A) hepatic impairment can be safely treated with a combination regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir without dose adjustment. Also, no dose adjustment is expected to be required for the 3-DAA regimen in HCV-infected subjects with decompensated cirrhosis (Child-Pugh B); the safety and efficacy data from the ongoing clinical study will be used to further confirm the dosing recommendations for this patient population. Treatment of HCV-infected patients with severe (Child-Pugh C) hepatic impairment is not recommended due to substantially elevated exposures of paritaprevir and dasabuvir.

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Conflict of interest

A.K., R.M.M., T.J.P., V.M.M., B.D., W.M.A., B.M.B., and S.D., are employees of AbbVie, Inc. and may hold stock and/or stock options. T.C.M. is an employee of Orlando Clinical Research Center, Orlando, Florida. E.J.L. is the Vice President of Scientific and Research Development at the Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX, USA. He has received research/grant support from AbbVie Inc., Achillion Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Idenix Pharmaceuticals, Janssen, Merck & Co., Novartis, Presidio, Roche, Santaris Pharmaceuticals, Theravance, and Vertex Pharmaceuticals. He has been a speaker for AbbVie Inc., Gilead Sciences, Janssen, Kadmon, Merck & Co., and Vertex Pharmaceuticals and is an advisor/consultant for AbbVie Inc., Achillion Pharmaceuticals, BioCryst, Biotica, Bristol-Myers Squibb, Enanta, Gilead Sciences, Idenix Pharmaceuticals, Janssen, Merck & Co., Novartis, Santaris Pharmaceuticals, Regulus, Theravance, and Vertex Pharmaceuticals.

Author's contributions

A.K., R.M.M., T.J.P., B.D., W.M.A., B.M.B., and S.D. contributed to the study design and analysis and interpretation of the data. T.C.M., E.J.L., and V.M.M. contributed to data acquisition and study supervision. All authors participated in the drafting and revising of the manuscript.

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