

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
<p>Name of Study Drug: paritaprevir/ritonavir/ombitasvir, dasabuvir (ABT-450/r/ABT-267, ABT-333)</p>	<p>Volume:</p> <p>Page:</p>	
<p>Name of Active Ingredient: Paritaprevir (ABT-450): (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{{(5-methylpyrazin-2-yl)carbonyl}amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4] diazacyclopentadecine-14a(5H)-carboxamide dihydrate Ritonavir: [5S-(5R*,8R*,10R*,11R*)]10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid,5-thiazolylmethyl ester Ombitasvir (ABT-267): Dimethyl ([(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbonyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate Dasabuvir (ABT-333): Sodium 3-(3-tert-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1).</p>		

Title of Study: An Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Treatment-Naïve and Treatment-Experienced Asian Adults with GT1b Chronic Hepatitis C Virus (HCV) Infection and Compensated Cirrhosis	
Coordinating Investigator: ██████████	
Study Sites: A total of 32 study sites (21 in China, 6 in South Korea, and 5 in Taiwan) were activated for the study; 30 sites enrolled subjects, and 2 study sites (1 in China and 1 in South Korea) did not enroll any subjects.	
Publications: One published abstract.	
Studied Period (Years): First Subject First Visit: 20 July 2015 Last Subject Last Visit: 16 March 2017	Phase of Development: 3
Objectives: The primary objectives of the study were to assess the safety and to compare the percentage of subjects achieving sustained virologic response at Post-Treatment Week 12 (SVR ₁₂ [HCV ribonucleic acid (RNA), < lower limit of quantification (LLOQ), 12 weeks following therapy]) and the percentage of subjects achieving sustained virologic response at Post-Treatment Week 24 (SVR ₂₄ [HCV RNA < LLOQ, 24 weeks following therapy]; SVR ₂₄ is for regulatory submission in China only) following 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 coadministered with RBV to the historical SVR rate of telaprevir (TVR) plus pegylated interferon (pegIFN) and RBV therapy in HCV genotype (GT)1b-infected cirrhotic adults. The secondary objectives of this study were to demonstrate the effect of the direct-acting antiviral (DAA) combination regimen on HCV RNA levels during and after treatment as measured by on treatment virologic failure and post-treatment relapse, respectively.	
Methodology: This was a Phase 3, open-label, multicenter study designed to evaluate the efficacy and safety of ABT-450/r/ABT-267 and ABT-333 (3-DAA) coadministered with RBV for 12 weeks in HCV GT1b-infected adults with compensated cirrhosis who were treatment-naïve or HCV treatment-experienced with interferon-based (IFN [alpha, beta, or pegIFN]) therapy with RBV. Treatment consisted of ABT-450/r/ABT-267 150/100/25 mg once daily + ABT-333 250 mg twice daily (3-DAA) + weight-based RBV for 12 weeks. Subjects weighing < 75 kg were to receive RBV 1000 mg daily divided twice daily, and subjects weighing ≥ 75 kg were to receive RBV 1200 mg daily divided twice daily. This study consisted of a Treatment Period and a Post-Treatment Period. During the Treatment Period, subjects received treatment with 3-DAA co-administered with RBV for 12 weeks. Upon completing the Treatment Period or premature discontinuation of the Treatment Period, subjects entered the 48-week Post-Treatment Period. As this was an open-label study, safety and efficacy evaluations occurred throughout the Treatment and Post-Treatment Periods. Safety evaluations were also performed by a Data Monitoring Committee. Reported herein are results of all analyses of data collected through Post-Treatment Week 48.	

Number of Subjects (Planned and Analyzed):

Approximately 100 subjects were planned to be enrolled, with a minimum of 35 treatment-naïve and 35 treatment-experienced subjects (approximately 60 subjects from sites in China and 20 subjects each from sites in South Korea and Taiwan). A total of 104 subjects were enrolled (63 in China, 21 in South Korea, and 20 in Taiwan).

Diagnosis and Main Criteria for Inclusion:

Subjects were adults of Chinese, South Korean, or Taiwanese decent with full Chinese, South Korean, or Taiwanese parentage (18 to 70 years of age, inclusive). Subjects had a chronic HCV GT1b infection, plasma HCV RNA > 1000 IU/mL, and documentation of cirrhosis (e.g., a Metavir score > 3 or an Ishak score > 4) or FibroScan[®] result \geq 14.6 kPa. Subjects were treatment-experienced or treatment-naïve. The treatment-experienced subjects were defined as follows:

- Non-responder: Received at least 12 weeks of IFN (alpha, beta or pegIFN) with RBV therapy for the treatment of HCV and failed to achieve undetectable HCV RNA (HCV RNA < lower limit of detection) at the end of treatment, or
- Relapser: Received IFN (alpha, beta or pegIFN) with RBV therapy for the treatment of HCV and was undetectable at or after the end of treatment, but subsequently had detectable HCV RNA within 24 weeks of treatment follow-up; or
- IFN-based therapy (IFN [alpha, beta or pegIFN] with RBV) intolerant: treatment of HCV was discontinued during the treatment period due to intolerance to any of the components of the IFN based therapy (IFN [alpha, beta or pegIFN] with RBV) therapy.

Females were either practicing total abstinence from sexual intercourse, sexually active with female partners only, postmenopausal for at least 2 years, surgically sterile, or of childbearing potential and practicing 2 effective forms of birth control while receiving study drug. Males must have been surgically sterile, had male partners only, or agreed to practice 2 effective methods of birth control throughout the course of the study.

Subjects were excluded if they had any of the following laboratory values at Screening: alanine aminotransferase (ALT) > 7 \times upper limit of normal (ULN), aspartate aminotransferase > 7 \times ULN, albumin < 2.8 g/dL, hemoglobin < lower limit of normal, total bilirubin \geq 3.0 mg/dL, and platelets < 60,000 cells per mm³. Subjects were also excluded if they had any current or past clinical evidence of Child-Pugh B or C classification or clinical history of liver decompensation or if they had confirmed presence of hepatocellular carcinoma.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:					
Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
ABT-450/ Ritonavir/ABT-267	AbbVie	Oral	Tablet	75 mg/50 mg/ 12.5 mg	14-005707
ABT-333	AbbVie	Oral	Tablet	250 mg	14-005080
Ribavirin					
South Korea and Taiwan	Roche or Generic Manufacturer	Oral	Tablet	200 mg	14-006933
China	Shanghai Sine Tianping Pharmaceutical Co., Ltd	Oral	Tablet	100 mg	15-003296
Duration of Treatment: Subjects received ABT-450/r/ABT-267 and ABT-333 with RBV for 12 weeks.					
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Not applicable.					
Criteria for Evaluation					
Efficacy:					
HCV RNA in IU/mL was assessed at all Treatment Period visits and at all Post-Treatment visits.					
The primary endpoints were the percentage of subjects with SVR ₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) and the percentage of subjects with SVR ₂₄ (HCV RNA < LLOQ 24 weeks after the last actual dose of study drug) (SVR ₂₄ was a primary endpoint for regulatory submission in China only).					
The secondary endpoints were the percentage of subjects with on-treatment virologic failure, the percentage of subjects with relapse by Post-Treatment Week 12, and the percentage of subjects with relapse by Post-Treatment Week 24.					
Resistance:					
For subjects receiving study drugs who experienced virologic failure (who had HCV RNA ≥ 1000 IU/mL), the variants at baseline at signature resistance-associated positions identified by population nucleotide sequencing compared to the prototypic reference sequence, the amino acid variants in available postbaseline samples identified by population nucleotide sequencing compared to the baseline sequence, and the amino acid variants in available postbaseline samples at signature resistance-associated positions identified by population nucleotide sequencing compared to the prototypic reference were to be summarized.					
Patient-Reported Outcomes:					
The change in general health and disease-specific Health Related Quality of Life (HRQoL) was assessed using the Short Form 36, version 2 (SF-36v2), HCV Patient Report Outcomes (HCV-PRO) instruments. Health State Utility was measured using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L).					

Criteria for Evaluation (Continued)

Pharmacokinetic:

Plasma concentrations of ABT-450, ABT-267, ritonavir, ABT-333, ABT-333 M1 metabolite, and RBV were determined at each study visit up to the end of treatment. Pharmacokinetic parameters including the maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), and area under the plasma concentration time curve (AUC) were determined by noncompartmental methods using data from subjects who participated in the intensive pharmacokinetic sampling. Trough plasma concentration (C_{trough}) was calculated by binning of the concentrations in time interval of > 22 to 26 hours for once daily drugs and > 10 to 14 hours for twice daily drugs based on time after the last dose across all visit after Week 2.

Safety:

Safety and tolerability were assessed by monitoring adverse events, physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECGs), and vital signs.

Statistical Methods

Efficacy:

For South Korea and Taiwan, the primary efficacy endpoint was:

- A1. SVR₁₂: Superiority to the historical SVR rate for TVR plus pegIFN/RBV therapy; the lower confidence bound (LCB) of the 95% confidence interval (CI) for the percentage of subjects with SVR₁₂ must have exceeded 67% to achieve superiority.

For China, the primary efficacy endpoints were:

- B1. SVR₁₂: Superiority to the historical SVR rate for TVR plus pegIFN/RBV therapy; the LCB of the 95% CI for the percentage of subjects with SVR₁₂ must have exceeded 67% to achieve superiority.
- B2. SVR₂₄: Superiority to the historical SVR rate for TVR plus pegIFN/RBV therapy; the LCB of the 95% CI for the percentage of subjects with SVR₂₄ must have exceeded 67% to achieve superiority.

For China, in order to control the Type I error rate at 0.05, a fixed-sequence testing procedure was used to proceed through the primary efficacy endpoints. That is, only if success was demonstrated for the primary endpoint of superiority of the SVR₁₂ rate to the historical rate for TVR plus pegIFN and RBV therapy (B1) would the testing continue to the second primary endpoint of superiority of the SVR₂₄ rate to the historical rate for TVR plus pegIFN and RBV therapy (B2).

To test the hypothesis that the percentage of treatment-naïve and IFN-based therapy (IFN [alpha, beta, or pegIFN] with RBV) treatment-experienced HCV GT1b-infected Asian subjects with compensated cirrhosis treated with ABT-450/r/ABT-267 + ABT-333 + RBV for 12 weeks who achieved SVR₁₂/SVR₂₄ is superior to a clinically meaningful threshold based on the historical SVR rates for the HCV GT1-infected population treated with TVR plus pegIFN/RBV, the percentage of subjects with SVR₁₂/SVR₂₄ was calculated along with a 2-sided 95% CI using the Wilson score method, and the LCB was compared to the defined threshold. The LCB of the 95% CI for the SVR₁₂/SVR₂₄ rate must have been greater than 67% in order for the regimen to be considered superior.

The percentages (with 2-sided 95% CIs using the Wilson Score method to the binomial distribution) of the subjects with on-treatment virologic failure and post-treatment relapse were calculated and summarized for the secondary endpoints.

Statistical Methods (Continued)

Resistance:

Only samples with an HCV RNA level of ≥ 1000 IU/mL were to undergo population sequence analysis in order to allow accurate assessment of the products of amplification. For subjects who experienced virologic failure, the sample closest in time after failure with an HCV RNA level ≥ 1000 IU/mL was used if the HCV RNA level at the time of failure would have been < 1000 IU/mL.

Patient-Reported Outcomes:

Exploratory analyses of patient-reported outcomes (PROs) included mean change from baseline to each applicable postbaseline visit in SF-36v2 Mental Component Summary and Physical Component Summary score, HCV-PRO total score, and EQ-5D-5L health index score and Visual Analogue Scale score. The minimally important difference (MID) for the change from Baseline to Final Treatment Visit in the SF-36v2 Physical Component Summary and Mental Component Summary was prespecified as -5 units. For the HCV-PRO total score and the EQ-5D-5L health index score, the MID was defined by receiver operating characteristic analysis using the SF-36v2 Mental Component Summary and Physical Component Summary as anchor scores. The percentage of subjects without a decrease from baseline to the Final Treatment Visit that was greater than or equal to the MID was calculated for these scores.

Pharmacokinetic:

Plasma concentrations of ABT-450, ABT-267, ABT-333, ABT-333 M1 metabolite, ritonavir, and RBV were tabulated and summarized for each time and study visit. Pharmacokinetic parameters (C_{\max} , T_{\max} , and AUC) of ABT-450, ABT-267, ABT-333, ABT-333 M1 metabolite, ritonavir, and RBV were summarized.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. The number and percentage of subjects with treatment-emergent adverse events (TEAEs) were tabulated by primary MedDRA system organ class (SOC) and preferred term. The tabulation of the number of subjects with TEAEs by severity rating and relationship to study drug was provided. In addition, the number and percentage of subjects with serious TEAEs and the number and percentage of subjects with TEAEs leading to study drug discontinuation were also provided.

Clinical laboratory tests were summarized at each study visit. The baseline value was the last measurement prior to the initial dose of study drug. Mean changes from baseline to each postbaseline visit were summarized. The number and percentage of subjects with postbaseline values meeting prespecified criteria for potentially clinically significant (PCS) laboratory values as well as per grade levels during treatment were summarized.

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each postbaseline visit were summarized. Frequencies and percentages of subjects with postbaseline values meeting predefined criteria for PCS vital signs values during treatment were summarized.

Summary/Conclusions

Efficacy Results:

A primary objective of the study was to compare the SVR₁₂ and SVR₂₄ (SVR₂₄ for China only) rates of 12 weeks of treatment with 3-DAA + RBV to the historical SVR rate of TVR plus pegIFN and RBV therapy.

The SVR₁₂ and SVR₂₄ rates were 100% (104/104) with a 95% CI of 96.4%, 100.0%. Therefore, the lower bound of the 95% CI was above 67% (superiority threshold), and the SVR₁₂ and SVR₂₄ rates with 3-DAA + RBV for 12 weeks demonstrated superiority to the historical control rate for TVR plus pegIFN and RBV therapy in HCV GT1b-infected subjects with compensated cirrhosis. Sensitivity analyses that evaluated alternative methods to impute missing post-treatment virologic results yielded SVR₁₂ and SVR₂₄ rates that were consistent with the primary analyses.

The SVR₁₂ and SVR₂₄ rates (n/N, 95% CIs) were 100% (63/63, 94.3%, 100.0%) in subjects from China, 100% (21/21, 84.5%, 100.0%) in subjects from South Korea; and 100% (20/20, 83.9%, 100.0%) in subjects from Taiwan. Therefore, the LCBs for the 95% CIs of the SVR₁₂ and SVR₂₄ rates from each geographic region were above the historical TVR plus pegIFN and RBV therapy threshold of 67%. In addition, the LCBs of each geographic region's 95% CIs for the primary endpoints were higher than the geographic region-specific historical SVR rates of the standard of care pegIFN/RBV.

No subject experienced relapse throughout the 48-week Post-Treatment Period.

Resistance Results:

All of the subjects achieved SVR₁₂ and SVR₂₄ thus, no resistance testing was conducted.

Patient-Reported Outcome Results:

The majority of subjects did not report any decreases that met MID values in their HRQoL, function, or well-being (per SF-36v2 Mental Component Summary, Physical Component Summary, EQ-5D-5L health index, and HCV-PRO total scores) at the end of treatment.

Pharmacokinetic Results:

Exposures of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, and RBV were comparable between Chinese, South Korean, and Taiwanese HCV GT1b-infected subjects with compensated cirrhosis.

Safety Results:

A primary objective of the study was to assess the safety of 12 weeks of treatment with 3-DAA + RBV. Administration of 3-DAA + RBV for 12 weeks to HCV GT1b-infected adults with compensated cirrhosis was generally well tolerated. The majority of subjects (82.7%) reported at least 1 TEAE. The maximum severity of TEAEs reported was mild in the majority of subjects, and 2 subjects reported severe TEAEs (1.9%). One subject prematurely discontinued study drug due to a TEAE.

The most common ($\geq 10\%$) TEAEs among all subjects were blood bilirubin increased (25.0%), pruritus (15.4%); anemia (14.4%); asthenia, bilirubin conjugated increased, and blood bilirubin unconjugated increased (each 11.5%); and dizziness and fatigue (each 10.6%).

The overall incidence of serious TEAEs was low (3.8%), and no commonality was evident among serious TEAEs. No serious TEAE was considered by the investigator or AbbVie to have a RP of being related to DAA treatment. No deaths were reported.

Summary/Conclusions (Continued)

Safety Results (Continued):

No subject in the present study experienced a TEAE that was identified as a hepatotoxicity-related adverse event. The only TEAE identified as bilirubin-related was ocular icterus, which occurred in 2.9% of subjects; none of these TEAEs was serious or led to premature discontinuation of study drug, interruption of study drug, or RBV dose modification. Similar to previous studies of 3-DAA + RBV, total bilirubin elevation, predominantly indirect bilirubin elevation, asymptomatic and transient, occurred in a subset of subjects. One (1.0%) subject experienced a confirmed postbaseline ALT elevation of $> 5 \times \text{ULN}$, which was asymptomatic and confounded by concurrent herbal supplement use. The subject achieved SVR₁₂ and SVR₂₄. The incidence of confirmed postbaseline ALT elevations of $> 5 \times \text{ULN}$ (1.0%) was comparable to those observed in studies of 3-DAA + RBV in Western subjects. In general, ALT or bilirubin elevations were not associated with each other or clinical symptoms. Bilirubin elevation, predominantly driven by indirect bilirubin, generally peaked at Week 1 and declined thereafter without requiring intervention. There were no Hy's law cases, and there were no reports of hepatic decompensation.

Analysis of rash-related events during this study also showed no new or different pattern compared with other clinical studies of 3-DAA when coadministered with RBV. Most of these TEAEs were assessed by the investigator as mild in severity and as having a reasonable possibility of being related to DAA and/or RBV treatment. No subject experienced a TEAE that was identified as a severe cutaneous reaction.

Grade 2 hemoglobin decreases ($< 100 \text{ g/L}$) occurred in 9.6% of subjects. No grade ≥ 3 ($< 80 \text{ g/L}$) hemoglobin decreases were observed. Ribavirin dose reductions occurred in 12.5% of all subjects, mostly for declines in hemoglobin (in 10.6% of all subjects). No subject required a blood transfusion or erythropoietin, nor did any subject discontinue study drug due to anemia or hemoglobin decrease during the study. No clinically meaningful results of urinalysis or vital signs were observed, and there were no observed, DAA-related, clinically significant ECG findings.

Conclusions:

In summary, SVR₁₂ and SVR₂₄ were achieved in 100% of subjects treated with 3-DAA + RBV for 12 weeks, regardless of prior treatment status or geographic region. The SVR₁₂ and SVR₂₄ rates demonstrated superiority to the historical threshold for TVR plus pegIFN and RBV therapy and were comparable to the SVR₁₂ rate in a previous global study of 3-DAA + RBV for 12 weeks in Western subjects with compensated cirrhosis. No subject experienced relapse throughout the 48-week Post-Treatment Period. The exposures of DAAs, ritonavir, and RBV were comparable between Chinese, South Korean, and Taiwanese HCV GT1b-infected subjects with compensated cirrhosis. The 3-DAA + RBV regimen was well tolerated with a low rate of TEAEs leading to premature discontinuation of study drugs, demonstrating a favorable safety profile, both overall and within each of the geographic regions of China, South Korea, and Taiwan, and is consistent with the profile observed in AbbVie's Global Phase 3 studies.