

2.0 Synopsis

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

<p>Title of Study: An Open-Label Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir With or Without Dasabuvir in Adults with Genotype 1a or Genotype 4 Chronic Hepatitis C Virus (HCV) Infection, With Severe Renal Impairment or End Stage Renal Disease (RUBY-II)</p>	
<p>Coordinating Investigator: Edward Gane, MD</p>	
<p>Study Sites: A total of 10 investigative sites in Australia, Europe, or New Zealand; 2 study sites did not enroll any subjects.</p>	
<p>Publications: 1 abstract</p>	
<p>Studied Period (Years): First Subject First Visit: 01 October 2015 Last Subject Last Visit: 05 December 2016</p>	<p>Phase of Development: 3b</p>
<p>Objectives: The primary objective of this study was to compare the safety and efficacy (the percentage of subjects achieving a 12-week sustained virologic response, SVR₁₂ [hepatitis C virus ribonucleic acid {HCV RNA} < lower limit of quantification {LLOQ} 12 weeks following treatment]) of co-formulated ombitasvir, paritaprevir, and ritonavir (ombitasvir/paritaprevir/ritonavir) co-administered with dasabuvir for 12 weeks (3-direct-acting antiviral agent [DAA] regimen) in treatment-naïve or (pegylated) interferon/ribavirin ([peg]IFN/RBV) treatment-experienced, noncirrhotic subjects with severe renal impairment (predialysis) or end-stage renal disease ([ESRD] on dialysis) with HCV genotype (GT)1a infection, or without dasabuvir for 12 weeks (2-DAA regimen) in treatment-naïve or (peg)IFN/RBV treatment-experienced subjects with HCV GT4 infection. The secondary objectives of this study were to assess the number and percentage of subjects with virologic failure during treatment and the number and percentage of subjects with relapse post-treatment.</p>	
<p>Methodology: This was a Phase 3b open-label, multicenter study evaluating the efficacy of the 3-DAA regimen for 12 weeks in treatment-naïve or (peg)IFN/RBV treatment-experienced subjects with HCV GT1a infection, or the 2-DAA regimen for 12 weeks in treatment-naïve or (peg)IFN/RBV treatment-experienced subjects with HCV GT4 infection, in noncirrhotic subjects with severe renal impairment or ESRD. The study was designed to enroll approximately 40 eligible subjects at approximately 15 sites, including approximately 30 subjects in Arm 1 (3-DAA regimen) and 10 subjects in Arm 2 (2-DAA regimen). The total number of treatment-experienced subjects was limited to approximately 33% of the total number enrolled. Within each arm, the number of subjects with chronic kidney disease (CKD) Stage 4 renal disease was limited to approximately 25% of the total number enrolled. The duration of the study was up to 36 weeks long (not including a screening period), consisting of a 12-week Treatment Period and a 24-week Post-Treatment Period. Upon completing the Treatment Period or premature discontinuation of the Treatment Period, subjects entered the 24-week Post-Treatment Period where they were monitored for safety, HCV viral load, and the emergence and/or persistence of resistant viral variants.</p>	

Number of Subjects (Planned and Analyzed):					
The study was originally designed to enroll a total of 40 subjects (30 subjects in Arm 1 and 10 subjects in Arm 2); however, the study enrollment goal was reduced to 20 total subjects due to the sites' inability to achieve the planned screening goal. A total of 18 subjects were enrolled (13 subjects in Arm 1 and 5 subjects in Arm 2) and received at least 1 dose of study drugs.					
Diagnosis and Main Criteria for Inclusion:					
Subjects were noncirrhotic adults infected with either HCV GT1a infection (Arm 1) or HCV GT4 infection (Arm 2). Subjects were either treatment-naïve or (peg)IFN/RBV treatment-experienced. Subjects had severe renal impairment or ESRD and had an estimated glomerular filtration rate < 30 mL/min/1.73 m ² , as estimated by the modification of diet in renal disease method. 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 1 protocol-specified form of birth control while receiving study drug. Males were to have been surgically sterile, had male partners only, or agreed to practice a protocol-specified form of birth control throughout the course of the study.					
Subjects were excluded if they had any of the following laboratory values at Screening: albumin < 3.5 g/dL, hemoglobin < 8 g/dL, total bilirubin ≥ 3.0 mg/dL, platelets < 120,000 cells per mm ³ , and international normalized ratio (INR) > 2.3. Subjects with a known inherited blood disorder and INR > 2.3 may have been enrolled with permission of the AbbVie Study Designated Physician. Subjects were also excluded if they had any current or past clinical evidence of cirrhosis, such as ascites or esophageal varices, or a prior biopsy showing cirrhosis or advanced bridging fibrosis.					
Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:					
Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
Ombitasvir/ paritaprevir/ ritonavir	AbbVie	Oral	Tablet	12.5 mg/ 75 mg/ 50 mg	14-002317
Dasabuvir	AbbVie	Oral	Tablet	250 mg	14-005917
Duration of Treatment:					
Subjects received either the 3-DAA regimen or the 2-DAA regimen for 12 weeks.					
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:					
Not applicable.					

Criteria for Evaluation

Efficacy:

Virologic response was assessed by HCV RNA in IU/mL at various time points from Day 1 through 24 weeks after completion of study drug treatment.

The primary efficacy variable was SVR₁₂ (HCV RNA < lower limit of quantification 12 weeks after the last actual dose of study drug).

The secondary efficacy variables were on-treatment virologic failure and post-treatment relapse.

Resistance:

The following resistance information was planned to be analyzed for subjects receiving study drugs who did not achieve SVR₁₂ and who had HCV RNA \geq 1000 IU/mL: 1) the variants at signature resistance-associated amino acid positions at baseline identified by population nucleotide sequencing and comparison to the appropriate prototypic reference sequence, 2) the amino acid variants in available post-baseline samples identified by population and/or clonal nucleotide sequencing and comparison to the baseline sequence, and 3) the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by population nucleotide sequencing and comparison to the appropriate prototypic reference sequence.

Pharmacokinetic:

Individual plasma concentrations of paritaprevir, ritonavir, ombitasvir, dasabuvir, and dasabuvir M1 metabolite were tabulated and summarized.

Values for the pharmacokinetic (PK) parameters of paritaprevir, ombitasvir, ritonavir, dasabuvir, and dasabuvir M1 metabolite including the maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), trough plasma concentration (C_{trough}), and area under the concentration-time curve (AUC) were determined by noncompartmental methods using data from subjects who participated in the intensive PK sampling.

Safety:

Safety and tolerability were assessed by monitoring adverse events, physical examinations, clinical laboratory tests, and vital signs.

Patient-Reported Outcomes:

Health state utility was measured using the EuroQol-5 Dimensions-3 Levels Health State Instrument (EQ-5D-3L) Questionnaire (including health state and visual analogue score).

Statistical Methods

Efficacy:

The primary endpoint was the percentage of subjects in each treatment arm with SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drugs). The number and percentage of subjects achieving SVR₁₂ were calculated and a 2-sided 95% Wilson score confidence interval (CI) for binomial proportion was computed.

In each treatment arm, the secondary efficacy endpoints were:

1. The percentage of subjects with on-treatment virologic failure during the Treatment Period (defined as confirmed HCV RNA \geq LLOQ after HCV RNA < LLOQ during treatment or confirmed increase from nadir in HCV RNA [2 consecutive HCV RNA measurements $> 1 \log_{10}$ IU/mL above nadir] at any time point during treatment or HCV RNA \geq LLOQ persistently during treatment with at least 6 weeks [≥ 36 days] of treatment),
2. The percentage of subjects with post-treatment relapse (defined as confirmed HCV RNA \geq LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment).
3. The numbers and percentages of the subjects with virologic failure during treatment and with Post-Treatment relapse were calculated. The corresponding 2-sided 95% Wilson score CIs for a binomial proportion were calculated.

Resistance:

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

The following analyses were to be performed on the samples from subjects who did not achieve SVR₁₂ and who had post-baseline resistance data available. The HCV amino acid sequence as determined by population sequencing at the time of virologic failure or treatment discontinuation, or the sample closest in time after failure/discontinuation with an HCV RNA level of ≥ 1000 IU/mL, are compared with the baseline and appropriate prototypic reference amino acid sequences. The number and percentage of subjects with emerged variants by amino acid position and variant within a DAA target in a treatment sample compared to baseline were to be summarized by HCV subtype. Linkage between emerged variants by population sequencing was also evaluated. A listing by subject and time point of the linked variants by population sequencing was to be provided.

Pharmacokinetic:

Plasma concentrations of paritaprevir, ombitasvir, dasabuvir, dasabuvir M1 metabolite, and ritonavir were tabulated and summarized.

For subjects who participated in the intensive PK sampling, values for the PK parameters including the C_{max}, T_{max}, C_{trough}, and AUC were summarized and tabulated for each analyte.

Statistical Methods (Continued)

Safety:

The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by primary Medical Dictionary for Regulatory Activities (MedDRA[®]) system organ class and preferred term. Tabulations were also provided in which the number of subjects reporting an adverse event (MedDRA preferred term) was presented by severity (mild, moderate, or severe) and relationship to study drugs.

Change from baseline in laboratory tests and vital sign measurements to each time point of collection were summarized. Laboratory test and vital sign values that were potentially clinically significant (PCS) according to predefined criteria were identified, and the number and percentage of subjects with PCS values were calculated. Hemoglobin and liver function tests were also summarized by Common Terminology Criteria for Adverse Events grade.

Patient-Reported Outcomes:

Summary statistics (N, mean, SD, median, minimum, and maximum) of values at each visit and change from baseline to each visit were provided for the EQ-5D-3L health state and visual analogue scale scores.

Summary/Conclusions

Efficacy Results:

Noncirrhotic subjects with severe renal impairment or ESRD infected with HCV GT1a (Arm 1) or HCV GT4 (Arm 2) were treated with the 3-DAA and 2-DAA regimen, respectively, for 12 weeks. Sustained virologic response 12 weeks postdosing was achieved by 13/13 (100.0%) subjects in Arm 1 and 4/5 (80.0%) subjects in Arm 2. There were no on-treatment virologic failures or post-treatment relapses. The 1 subject in Arm 2 that did not achieve SVR₁₂ elected to discontinue prematurely from the study to undergo kidney transplant and was therefore classified as a nonresponder.

Resistance Results:

No subjects in the study experienced on-treatment virologic failure or relapse, and the single subject who discontinued early did not have a post-baseline sample with an HCV RNA level of ≥ 1000 IU/mL); therefore, no resistance testing was performed.

Pharmacokinetic Results:

For HCV-infected subjects with Stage 4 CKD or ESRD on dialysis, the exposures of the DAAs and ritonavir in this study were generally comparable to those in the RUBY-I study, further supporting that no dose adjustment is necessary for the DAAs when administered to HCV infected subjects with Stage 4 CKD or ESRD on dialysis.

Summary/Conclusions (Continued)

Safety Results:

The 3-DAA and 2-DAA regimens for 12 weeks were generally well tolerated in noncirrhotic, treatment-naïve or (peg)IFN/RBV treatment-experienced subjects with severe renal impairment or ESRD and with HCV GT1a or GT4 infection, respectively. The most common treatment-emergent adverse events (TEAEs) were abdominal pain, diarrhea, nausea, fatigue, and hypertension. There were 4 subjects who experienced serious adverse events (SAEs) with 1 subject in Arm 1 experiencing the SAEs of folliculitis and abdominal pain that were considered by the investigator to be treatment related. The SAE of folliculitis and nonserious AE of elevated transaminases led to discontinuation of study treatment. Another subject experienced the SAE of grade 4 ESRD leading to an elective kidney transplant and early discontinuation of study drug. There were no deaths in the study. Seven (38.9%) subjects experienced grade 2 hemoglobin decreases, and 2 (11.1%) subjects experienced grade 3 alanine aminotransferase elevations. There were no grade 2 or higher elevations of aspartate aminotransferase or total bilirubin. No new safety signals were observed in this study.

Conclusions:

In summary, the 3-DAA regimen in HCV GT1a-infected subjects and the 2-DAA regimen in HCV GT4-infected subjects with severe renal impairment or ESRD were well-tolerated and highly efficacious in this small, open-label, baseline-controlled study. All subjects that completed study treatment achieved SVR₁₂. No new safety signals were identified. These data support the hypothesis that ombitasvir/paritaprevir/ritonavir and ombitasvir/paritaprevir/ritonavir with dasabuvir may have potential as treatment options for patients with HCV GT4 or GT1 infection, respectively, in the setting of severe renal impairment or ESRD.