

2.0 Synopsis

<p>AbbVie Inc.</p>	<p>Individual Study Table Referring to Part of Dossier:</p>	<p>(For National Authority Use Only)</p>
<p>Name of Study Drug: Ombitasvir/paritaprevir/ritonavir, dasabuvir, ribavirin</p>	<p>Volume:</p> <p>Page:</p>	
<p>Name of Active Ingredient: Ombitasvir: Dimethyl ([[(2<i>S</i>,5<i>S</i>)-1-(4-<i>tert</i>-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diyl}carbonyl(2<i>S</i>)pyrrolidine-2,1-diyl][(2<i>S</i>)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate 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>,14,15,16,16a-tetradecahydrocyclopropa[<i>e</i>]pyrrolo[1,2-<i>a</i>][1,4]diazacyclopentadecine-14<i>a</i>(5<i>H</i>)-carboxamide hydrate 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 dasabuvir: Sodium 3-(3-<i>tert</i>-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2<i>H</i>-pyrimidin-1-ide hydrate (1:1:1) ribavirin: 1-β-D-ribofuranosyl-1<i>H</i>-1,2,4-triazole-3-carboxamide</p>		

<p>Title of Study: An Open-Label Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with or without Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection, with Severe Renal Impairment or End Stage Renal Disease (RUBY-I)</p>	
<p>Coordinating Investigator: Eric J. Lawitz, MD</p>	
<p>Study Sites: 16 investigative sites in the United States.</p>	
<p>Publications: 4 abstracts.</p>	
<p>Studied Period (Years): First Subject First Visit: 23 September 2014 Last Subject Last Visit: 06 December 2016</p>	<p>Phase of Development: 3b</p>
<p>Objectives: The primary objective of this study was to assess the safety and efficacy (the percentage of subjects achieving a 12-week sustained virologic response, SVR₁₂ [HCV RNA < lower limit of quantification {LLOQ} 12 weeks following treatment]) of co-formulated ombitasvir, paritaprevir and ritonavir (ombitasvir/paritaprevir/ritonavir) and dasabuvir with or without RBV for 12 or 24 weeks in chronic HCV genotype 1-infected treatment-naïve or previous pegylated interferon (pegIFN)/RBV treatment-experienced adult subjects, with or without compensated cirrhosis, who had severe renal impairment (pre-dialysis) or end stage renal disease (on hemodialysis or peritoneal dialysis). The secondary objectives of this study were to assess direct-acting antiviral agent (DAA) pharmacokinetics in subjects with severe renal impairment including those on dialysis and to assess the number and percentage of subjects with virologic failure during treatment and the percentage of subjects with relapse post-treatment.</p>	
<p>Methodology: This was an open-label, multicenter study evaluating the efficacy of ombitasvir/paritaprevir/ritonavir and dasabuvir with or without RBV for 12 or 24 weeks in HCV GT1-infected, treatment-naïve or previous pegIFN/RBV treatment-experienced adults with or without compensated cirrhosis who have severe renal impairment or end-stage renal disease. This study consisted of two parts, Cohort 1 and Cohort 2. Approximately 70 eligible subjects were to be enrolled at approximately 15 sites. Subjects were to be categorized at baseline as having stage 4 or stage 5 renal disease. Cohort 1 was designed to evaluate the safety and efficacy of ombitasvir/paritaprevir/ritonavir and dasabuvir with or without RBV for 12 weeks in approximately 20 subjects without cirrhosis. HCV GT1a-infected, treatment-naïve, renally impaired subjects without cirrhosis received treatment with ombitasvir/paritaprevir/ritonavir and dasabuvir coadministered with RBV for 12 weeks (Arm A) and HCV GT1b-infected, treatment-naïve, renally impaired subjects without cirrhosis received treatment with ombitasvir/paritaprevir/ritonavir and dasabuvir for 12 weeks (Arm B). An aggregate review of available safety, efficacy and pharmacokinetic (PK) data was conducted after the last subject completed 12 weeks of treatment prior to initiating Cohort 2.</p>	

Methodology (Continued):

Cohort 2 was designed to evaluate the safety and efficacy of ombitasvir/paritaprevir/ritonavir and dasabuvir with or without RBV for 12 or 24 weeks in approximately 50 additional subjects, including subjects with or without cirrhosis. For Cohort 2, inclusion of RBV and treatment duration was determined based on review of data from Cohort 1. According to a pre-specified criterion, RBV was not to be administered in Cohort 2 if four or more subjects receiving RBV in Cohort 1 experienced a post baseline hemoglobin value < 8.0 g/dL in the absence of another identified etiology. Since this criterion was not met, and since RBV had been generally well tolerated in Cohort 1, RBV was administered in Cohort 2 to all subjects with GT1a infection. HCV GT1a-infected subjects without cirrhosis were to receive treatment with ombitasvir/paritaprevir/r and dasabuvir co-administered with RBV for 12 weeks (Arm C). HCV GT1a-infected subjects with cirrhosis were to receive treatment with ombitasvir/paritaprevir/r and dasabuvir coadministered with RBV for 24 weeks (Arm D). HCV GT1b-infected subjects with or without cirrhosis were to receive treatment with ombitasvir/paritaprevir/ritonavir and dasabuvir for 12 weeks (Arm E).

The duration of the study was up to 36 – 48 weeks long (not including the screening period), consisting of a 12-week Treatment Period (Cohort 1 and Arms C and E of Cohort 2) or a 24-week Treatment Period (Arm D of Cohort 2) 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.

As this was an open-label study, safety and efficacy evaluations occurred throughout the Treatment and Post-Treatment Periods.

Two interim analyses were originally planned for this study. The first interim analysis was conducted after all subjects in Cohort 1 (Arms A and B) had reached Post-Treatment Week 12 or prematurely discontinued the study. The second interim analysis was to be conducted after all subjects in Cohort 2 (Arms C, D and E) reached Post-Treatment Week 12 or prematurely discontinued the study. The second interim analysis was not conducted because there was no planned submission of a labeling variation.

Number of Subjects (Planned and Analyzed):

Approximately 70 subjects (20 subjects in Cohort 1 and 50 subjects in Cohort 2) were planned to be enrolled. Sixty-eight subjects were enrolled and received at least 1 dose of study drug (20 in Cohort 1 and 48 in Cohort 2).

Diagnosis and Main Criteria for Inclusion:

Cohort 1 subjects were HCV genotype 1-infected, treatment-naïve adults (at least 18 years of age) without cirrhosis and with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² as estimated by the modification of diet in renal disease (MDRD) 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 2 effective forms of birth control while receiving study drug. Males were to have been surgically sterile, had male partners only, or agreed to practice 2 effective methods of birth control throughout the course of the study.

Diagnosis and Main Criteria for Inclusion (Continued):

Cohort 2 subjects were to be HCV genotype 1-infected, treatment-experienced or treatment-naïve adults (at least 18 years of age) with or without cirrhosis and with an eGFR < 30 mL/min/1.73 m² as estimated by the MDRD method. Females were to be 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 were required to be surgically sterile, have male partners only, or agree 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: albumin < 2.8 g/dL, hemoglobin < 10 g/dL, total bilirubin ≥ 3.0 mg/dL, platelets < 25,000 cells per mm³, and international normalized ratio (INR) > 2.3. Subjects with a known inherited blood disorder and INR > 2.3 may be enrolled with permission of the AbbVie Study Designated Physician. 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 such as ascites (noted on physical exam), variceal bleeding or hepatic encephalopathy.

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	13-001960
Dasabuvir	AbbVie	Oral	Tablet	250 mg	12-007842
Ribavirin	Roche or Generic Manufacturer	Oral	Tablet	200 mg	14-001215

Duration of Treatment:

Cohort 1: Subjects received ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily (QD) and dasabuvir 250 mg twice daily (BID) with and without RBV 200 mg QD for 12 weeks.

Cohort 2: Subjects are to receive ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD and dasabuvir 250 mg BID with and without RBV 200 mg QD for 12 weeks or 24 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.

Resistance:

For subjects receiving study drugs who did not achieve SVR₁₂, the variants at signature resistance-associated amino acid positions by population nucleotide sequencing at baseline compared to the appropriate prototypic reference sequence, the variants at each amino acid position by population and/or clonal nucleotide sequencing at available post-baseline time points compared to the baseline sequence, and the variants at signature resistance-associated amino acid positions at available post-baseline time points by population and/or clonal nucleotide sequencing compared to the appropriate prototypic reference sequence were tabulated and summarized.

Pharmacokinetic:

Individual plasma concentrations of paritaprevir, ritonavir, ombitasvir, dasabuvir, dasabuvir M1 metabolite, and RBV were determined. Trough plasma concentrations, based on binning the sparse samples by time interval, were calculated for all subjects for whom data were available.

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

Safety:

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

Statistical Methods

Efficacy:

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

The secondary efficacy endpoints were: 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 (two 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) and 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).

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 confidence intervals for a binomial proportion were calculated.

Statistical Methods (Continued)

Resistance:

The following resistance information was provided for any SVR₁₂-achieving subject who had sequencing performed on baseline samples: the variants at signature amino acid positions at baseline identified by population nucleotide sequencing and comparison to the appropriate prototypic reference sequence.

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

Pharmacokinetic:

Plasma concentrations of ombitasvir, paritaprevir, dasabuvir, dasabuvir M1 metabolite, ritonavir, and RBV were tabulated for each subject and group. Summary statistics were computed by group (CKD stage).

For the intensive PK data, values for the pharmacokinetic parameters including C_{max}, T_{max}, C_{trough}, and AUC were calculated and tabulated for each analyte. Summary statistics were computed if more than 2 subjects were available in each group.

Pharmacokinetic parameters of ombitasvir, paritaprevir, ritonavir, dasabuvir, dasabuvir M1 metabolite, and RBV were compared in subjects receiving hemodialysis between dialysis and nondialysis days, as well as in subjects with Stage 4 severe renal impairment versus Stage 5 ESRD.

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.

Summary/Conclusions

Efficacy Results:

Subjects with Stage 4 or Stage 5 CKD, including those on hemodialysis, received the 3-DAA regimen of co-formulated ombitasvir/paritaprevir/ritonavir (25/150/100 mg once daily) and dasabuvir (250 mg twice daily) with RBV (dosed at 200 mg QD) for HCV GT1a-infected subjects for 12 or 24 weeks or without RBV for HCV GT1b-infected subjects for 12 weeks. SVR₁₂ was achieved by 64/68 (94.1%) subjects, with a 95% CI of 85.8% to 97.7%.

There were no on-treatment virologic failures and 1 subject experienced relapse at Post-Treatment Week 4.

The SVR₁₂ rates observed in each subgroup of the intent-to-treat (ITT) Population were consistent with that observed for the overall ITT population. All subjects who achieved SVR₁₂ also achieved SVR₂₄.

Summary/Conclusions (Continued)

Resistance Results:

One GT1a-infected subject in Arm A (Subject 1102) experienced relapse at Post-Treatment Week 4. At baseline this subject had Q80K in NS3, but had no other variants at signature amino acid positions in NS3, NS5A or NS5B. Treatment-emergent substitutions D168V in NS3, and Q30R in NS5A were present at the time of virologic failure in this subject. Additionally, M28T in NS5A was detected at Post-Treatment Week 24. Treatment-emergent NS3-D168V or NS5A-Q30R were not detected at Post-Treatment Week 24.

Pharmacokinetic Results:

The exposures of DAAs and ritonavir in HCV-infected subjects with ESRD on dialysis (Stage 5 CKD), regardless of dialysis day, were generally comparable to those in subjects with severe renal impairment (Stage 4 CKD). The DAAs and ritonavir do not appear to be extracted during hemodialysis. These data support that no dose adjustment is necessary for the DAAs when administered to HCV-infected subjects with Stage 4 CKD or ESRD on dialysis.

Safety Results:

A total of 59 (86.8%) subjects experienced at least 1 treatment-emergent adverse event. The most common ($\geq 10.0\%$ of total subjects) adverse event was anemia followed by fatigue, diarrhea, nausea, vomiting, hemoglobin decreased, and headache.

Forty (58.8%) subjects experienced at least 1 moderate or severe treatment-emergent adverse event, the most common ($\geq 10.0\%$ of total subjects) of which was anemia (20.6%) followed by diarrhea and nausea (10.3% each). Anemia, diarrhea and nausea were not reported in Arms B + E, arms in which subjects did not receive RBV. Fourteen (20.6%) subjects experienced at least 1 severe treatment-emergent adverse event. Aside from severe anemia reported in 2 Arm C subjects (2.9%), all severe adverse events were reported by a single subject each. Adverse events reported as having a reasonable possibility of being DAA-related occurred in 35 subjects (51.5%), with fatigue the most common adverse event followed by diarrhea, headache, nausea, and pruritus. Adverse events reported by the Investigator as having a reasonable possibility of being RBV-related occurred in 39 subjects (57.4%), with anemia the most common adverse event followed by fatigue, nausea, hemoglobin decreased, and diarrhea.

Seventeen subjects experienced 1 or more treatment-emergent serious adverse events, 2 of which were assessed as having a reasonable possibility of being related to study treatment (1 to ombitasvir/paritaprevir/ritonavir and dasabuvir and 1 to RBV). One subject (Arm D) had a severe, serious adverse event of volvulus that resulted in premature discontinuation of study drug and discontinuation from the study. The event, which resolved within 12 days, was assessed as having no reasonable possibility of being related to study treatment. One subject (Arm A) experienced a serious adverse event of left ventricular systolic dysfunction resulting in death 14 days after the end of treatment that was assessed as having no reasonable possibility of being related to ombitasvir/paritaprevir/r and dasabuvir or RBV. The subject had a had a relevant medical history of hypertension, ESRD, hemodialysis, ascites due to ESRD, fluid overload, pleural effusion, mild pulmonary hypertension with estimated left ventricular ejection fraction of 50% in the echocardiogram performed 1 year prior to enrollment, moderate left axis deviation (screening electrocardiogram) and prior cigarette smoking (1 pack for 35 years).

Summary/Conclusions (Continued)

Safety Results (Continued):

Ombitasvir/paritaprevir/ritonavir and dasabuvir with and without RBV was well tolerated in subjects with severe renal impairment, including those on hemodialysis, as evidenced by the fact that the only adverse event that led to discontinuation of the 3-DAA regimen was not considered treatment related, and the 1 serious adverse event considered to be possibly DAA-related did not result in study drug or study discontinuation. Hemoglobin reductions were common among subjects receiving RBV, and were managed primarily with RBV dose modification; 11 subjects (5 of whom had been treated with erythropoietin prior to baseline) were treated with erythropoietin and 2 subjects underwent blood transfusion. No new safety signals were observed.

Conclusions:

Ombitasvir/paritaprevir/ritonavir and dasabuvir with and without RBV was well tolerated and the subjects achieved an SVR₁₂ rate of 94.1%. There were no on-treatment virologic failures and 1 subject experienced post treatment relapse. All subjects who achieved SVR₁₂ also achieved SVR₂₄. Hemoglobin reductions were managed primarily with RBV dose modification.

No new safety signals were observed. The efficacy of ombitasvir/paritaprevir/r and dasabuvir appears comparable to that seen in subjects without severe renal disease in other Phase 3 studies. Available PK data suggest that ombitasvir, paritaprevir, dasabuvir, dasabuvir M1 metabolite and ritonavir exposures are also comparable and are not affected by hemodialysis. This supports the conclusion that no dose adjustment is necessary for the DAAs when administered to HCV infected subjects with severe renal impairment or end stage renal disease on dialysis.