2.0   Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier: Volume:	(For National Authority Use Only)
Name of Study Drug: Ombitasvir/paritaprevir/ritonavir, dasabuvir, ribavirin	**Page:**	
Name of Active Ingredient: Ombitasvir: Dimethyl ([(2*S*,5S)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate paritaprevir: (2*R*,6S,12Z,13a*S*,14a*R*,16a*S*)-*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(5*H*)-carboxamide hydrate 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 dasabuvir: 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) ribavirin: 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide		

Title of Study:	
An Exploratory Study to Evaluate the Kinetics of Viral Load Decline with Ombitasvir/Paritaprevir/Ritonavir (Ombitasvir/Paritaprevir/r) and Dasabuvir Therapy with Low Dose Ribavirin (RBV), Full Dose RBV or RBV Add-On in Treatment-Naïve Adults with Genotype 1a Chronic Hepatitis C Virus (HCV) Infection	
Coordinating Investigator: Andrew Talal, MD	
Study Site(s): 2 investigative sites in France and the United States. 2 global sites: 1 France, 1 United States	
Publications: None.	

Studied Period (Years):	**Phase of Development:** 2
First Subject First Visit: 23 June 2015	
Last Subject Last Visit: 06 December 2016	

Objective(s):

The primary objective of this study was to evaluate the effect of RBV on second phase plasma HCV RNA decline in subjects who received the 3-DAA regimen of ombitasvir/paritaprevir/r and dasabuvir with full-dose RBV compared to the 3-DAA regimen with low-dose RBV or without RBV in treatment-naive HCV GT1a-infected adult subjects.

Methodology:

This was a partially randomized, open-label, multicenter study evaluating the efficacy and safety of the combination of ombitasvir/paritaprevir/r and dasabuvir with low-dose RBV, full-dose (weight-based) RBV, or without RBV for 2 weeks with RBV added-on for the last 10 weeks of treatment, enrolling noncirrhotic HCV GT1a treatment-naïve subjects. The study consisted of a Screening period of up to 42 days, a 12-week Treatment Period (TP), and a 24-week Post-Treatment Period (PTP).

Number of Subjects (Planned and Analyzed):

The study was designed to enroll approximately 60 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. A total of 46 subjects were enrolled.

Diagnosis and Main Criteria for Inclusion:

The study population consisted of HCV GT1a-infected adult subjects without cirrhosis who were treatment-naïve.

The Main Criteria for Inclusion were:

1. Male or female at least 18 years of age at time of Screening.
2. Female who was:
   - practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle);
   - sexually active with female partners only;
   - not of childbearing potential, defined as:
   - postmenopausal for at least 2 years prior to Screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone (FSH) level indicating a postmenopausal state), or

Diagnosis and Main Criteria for Inclusion (Continued):

The Main Criteria for Inclusion were (Continued):

- surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or had a vasectomized partner(s);
- of childbearing potential and sexually active with male partner(s):
  - currently using at least 1 effective method of birth control at the time of Screening; and
  - agreed to practice 2 effective methods of birth control while receiving study drugs (as outlined in the subject information and consent form or other subject information documents), starting with Study Day 1 and for 7 months after stopping study drug, or as directed by the local RBV label. (Note: Ethinyl estradiol-containing hormonal contraceptives, including oral, implantable, and ring varieties, were not to be used during study drug treatment).

3. Males who were not surgically sterile who were sexually active with female partner(s) of childbearing potential agreed to practice 2 effective forms of birth control (as outlined in the subject information and consent form or other subject information documents) throughout the course of the study, starting with Study Day 1 and for 7 months after stopping study drug, or as directed by the local RBV label.

4. Chronic HCV infection prior to study enrollment. Chronic HCV infection was defined as 1 of the following:
   - Positive for anti-HCV Ab or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or
   - HCV RNA > 1,000 IU/mL at the time of Screening with a liver biopsy (current or past) consistent with chronic HCV infection (or a liver biopsy performed prior to enrollment with evidence of chronic hepatitis C disease).

5. Screening laboratory result indicating HCV GT1a infection.

The Main Criteria for Exclusion Included:

1. Women who were pregnant or breastfeeding.

2. Positive test result for Hepatitis B surface antigen (HbsAg) or anti-human immunodeficiency virus (HIV) positive immunoassay.

3. Use of any medications listed below, as well as those that were contraindicated for ritonavir and RBV, within 2 weeks prior or 10 half-lives whichever is longer, prior to study drug administration including but not limited to:

Alfuzosin	Fusidic Acid	Rifampin
Astemizole	Gemfibrozil	Salmeterol
Carbamazepine	Lovastatin	Sildenafil*
Cisapride	Methylergonovine	Simvastatin
Dihydroergotamine	Midazolam (oral)	St. John's Wort
Didanosine	Phenobarbital	Terfenadine
Efavirenz	Phenytoin	Triazolam
Ergotamine	Pimozide	
Ergonovine		
Ethinyl estradiol containing medications		

Diagnosis and Main Criteria for Inclusion (Continued):

The Main Criteria for Exclusion Included (Continued):

4. Use of known moderate or strong inducers of cytochrome P450 3A (CYP3A) or strong inducers of cytochrome P450 2C8 (CYP2C8) (e.g., phenobarbital, rifampin, carbamazepine, St. John's Wort) or strong inhibitors of CYP2C8 (e.g., gemfibrozil) within 2 weeks of the respective medication/supplement, prior to initial dose of study drug.

5. Use of anti-coagulants (i.e., warfarin or low-molecular-weight heparin) within 1 week of study start. Aspirin and antiplatelet drugs were stopped within 5 days of the study.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Numbers
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	13-005533, 13-002710, 14-005989, 14-006933

Duration of Treatment:

Subjects received treatment with ombitasvir/paritaprevir/r and dasabuvir co-administered with low-dose RBV or full-dose RBV for 12 weeks or without RBV for 2 weeks followed by full-dose RBV for the last 10 weeks.

Criteria for Evaluation

Efficacy:

Plasma HCV RNA in IU/mL and intrahepatic HCV RNA in copies/ng total RNA will be assessed at the indicated TP and PTP visits.

Pharmacokinetic:

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

Safety:

The following safety evaluations were analyzed during the study: adverse event monitoring and vital signs, physical examination, ECG, and laboratory tests assessments.

Statistical Methods

Efficacy:

All efficacy analyses were performed on the ITT population.

The primary endpoint was the slope of the second phase decline in plasma HCV RNA levels during treatment. The HCV viral kinetics in plasma during therapy were modeled through nonlinear mixed-effect models, including a rapid first phase of initial decline and a slower second phase decline. The slope of the second phase decline was estimated for each treatment arm. The slope was also compared between 3-DAA regimen with full dose RBV and 3-DAA regimen without RBV or with low-dose RBV using Wilcoxon's rank sum tests.

Pharmacokinetic:

Plasma concentrations of paritaprevir, ombitasvir, ritonavir, dasabuvir, dasabuvir M1 metabolite, and RBV were tabulated for each subject and treatment arm. Summary statistics were computed for each time point (for intensive PK data) or binned time interval (for sparse PK data).

For the intensive PK data, values for the pharmacokinetic parameters of ABT-450, ombitasvir, ritonavir, dasabuvir, and dasabuvir M1 metabolite, and RBV, including C_{max}, T_{max}, and AUC were calculated and tabulated for each analyte.

Safety:

All subjects who received at least 1 dose of study drug were included in the safety analyses.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that began or worsened in severity after initiation of study drug through 30 days post-study drug dosing) were tabulated by primary MedDRA system organ class (SOC) and preferred term for each treatment arm. The tabulation of the number of subjects with treatment-emergent adverse events by severity rating and relationship to study drug was also provided. Subjects reporting more than 1 adverse event for a given MedDRA preferred term were counted only once for that term using the most severe incident for the severity rating table and the most related for the relationship to study drug table. Subjects reporting more than 1 type of event within a SOC were counted only once for that SOC.

Clinical laboratory tests were summarized at each visit. The baseline value was the last measurement prior to the initial dose of study drug. Mean changes from baseline to each Post-Baseline Visit were summarized descriptively for each treatment arm.

Laboratory data values collected during the Treatment Period were categorized as low, normal, or high based on reference ranges of the laboratory used in this study. The number and percent of subjects who experienced post-baseline shifts during treatment in clinical laboratory values from low/normal to high and high/normal to low based on the normal range were summarized by treatment arm.

In addition, the number and percentage of subjects with post-baseline values meeting prespecified criteria for Potentially Clinically Significant laboratory values during treatment were summarized by treatment arm.

Vital sign measurements were summarized at each visit during the treatment period. Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each Post-Baseline Visit were summarized descriptively for each treatment arm. The baseline value was the last measurement prior to the initial dose of study drugs. Frequencies and percentages of subjects with post-baseline values meeting pre-defined criteria for Potentially Clinically Significant vital signs values during treatment were summarized by treatment arm.

Summary/Conclusions

Efficacy Results:

The primary efficacy analysis demonstrated that there was no significant difference in the effect of RBV on second phase plasma decline in subjects who received the 3-DAA regimen of ombitasvir/paritaprevir/r and dasabuvir with full-dose RBV (Arm B) compared to the 3-DAA regimen with low-dose RBV (Arm C) or without RBV for the first 2 weeks (Arm A). The median estimated slopes for the second phase plasma HCV RNA viral load decline were not statistically significantly different when Arm A was compared to Arm B ($P = 0.311$) or when Arm C was compared to Arm B ($P = 0.561$). High SVR_{12} rates were observed in all arms of the study: 85.7% for Arm A, 94.7% for Arm B, and 100% for Arm C.

Pharmacokinetic Results:

Across the 3 study arms, the exposures of DAAs and ritonavir were generally comparable. Ribavirin steady-state exposures in subjects receiving low-dose RBV QD dosing (Arm C) were approximately 50% lower than subjects receiving weight-based BID dosing (Arms A and B).

Safety Results:

The combination of ombitasvir/paritaprevir/r and dasabuvir without RBV for 2 weeks with RBV added-on for the last 10 weeks of treatment (Arm A), with full-dose (weight-based) RBV (Arm B), or with low-dose RBV (Arm C) in noncirrhotic HCV GT1a-infected treatment-naïve subjects was generally well tolerated. The most common TEAEs were procedural pain (from liver fine needle aspiration), fatigue, anemia, and pruritus. There were 2 treatment-emergent SAEs experienced by 1 subject (grade 4 depression and grade 4 drug dependence) with a history of depression and drug abuse. One subject prematurely discontinued study drug due to grade 2 hypertransaminasemia, which resolved upon discontinuation of study drug. Six subjects total (3 each in Arm A and Arm B) experienced TEAEs that led to RBV dose modifications (anemia [4 subjects] and hemoglobin decreased [2 subjects]), none of which were serious or required interruption of study drug. There were no TEAEs that led to interruption of study drug and no deaths in the study. A mean decline in hemoglobin values was observed across study arms, but these values returned to baseline values by the PT Wk 4 Visit. A few subjects had changes in liver function test values that met PCS criteria, but these elevations returned to normal values during the PT Period. No new safety signals were observed in this study.

Conclusions:

In conclusion, the 3-DAA regimen consisting of ombitasvir/paritaprevir/r and dasabuvir with full-dose RBV, low-dose RBV, or with add-on RBV (without RBV for first 2 weeks) are similar in their effects on second phase decline of plasma HCV RNA level and all 3 regimens produced high SVR_{12} rates. Across the 3 study arms, the exposures of DAAs and ritonavir were generally comparable. All 3 regimens were generally well-tolerated and had similar safety profiles. No clinically important trends or new safety signals were observed in any of the study arms.