

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 (OBV), paritaprevir (PTV), ritonavir (r), dasabuvir (DSV), ribavirin (RBV)</p>	<p>Volume:</p> <p>Page:</p>	
<p>Name of Active Ingredient:</p> <p>ombitasvir: Dimethyl ([(2S,5S)-1-(4-<i>tert</i>-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate</p> <p>paritaprevir: (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[<i>e</i>]pyrrolo[1,2-<i>a</i>][1,4]diazacyclopentadecine-14a(5H)-carboxamide dihydrate</p> <p>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</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>ribavirin: 1-β-D-ribofuranosyl-1<i>H</i>-1,2,4-triazole-3-carboxamide</p>		

Title of Study: An Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir With or Without Ribavirin (RBV) in US Veterans With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (TOPAZ-VA)	
Coordinating Investigator: Michael Fuchs, MD	
Study Sites: 10 sites in the United States (US) (and its territory, Puerto Rico)	
Publications: 1 (abstract)	
Studied Period (Years): First Subject First Visit: 13 May 2015 Last Subject Last Visit: 31 October 2016	Phase of Development: 3b
Objectives: The primary objectives of this study were to assess the safety and the sustained virologic response 12 weeks postdosing (SVR ₁₂) rate of OBV/PTV/r + DSV ± RBV for 12 or 24 weeks in HCV genotype (GT) 1-infected US veterans receiving healthcare through the Veterans Health Administration (VHA). The secondary objectives of this study were to assess the percentage of subjects with virologic failure during treatment, the percentage of subjects with relapse post-treatment, and the SVR ₁₂ rate among subjects with ongoing psychiatric disorders (defined as a clinical diagnosis of and requiring pharmacotherapy for depression, bipolar disorder, schizophrenia, anxiety, and/or post-traumatic stress disorder).	
Methodology: This was a Phase 3b, open-label, multicenter study evaluating the safety and efficacy of OBV/PTV/r + DSV ± RBV for 12 or 24 weeks in US veterans with chronic HCV GT1 infection and with or without compensated cirrhosis, who were either treatment-naïve or treatment-experienced, and who were receiving healthcare through the VHA. This study consisted of a Screening Period of up to 42 days, a 12- or 24-week Treatment Period, and a 24-week Post-Treatment (PT) Period. HCV GT1-infected subjects who were either treatment-naïve or treatment-experienced received OBV/PTV/r + DSV. Subjects with HCV GT1a infection and all GT1-infected subjects with compensated cirrhosis also received RBV. The treatment duration was 12 weeks for all subjects except HCV GT1a-infected subjects (including subjects with unknown or mixed GT1 subtype) with compensated cirrhosis who received treatment for 24 weeks. All subjects who received at least 1 dose of study drug were to be monitored for safety, HCV RNA, and the emergence and persistence of resistant viral variants for an additional 24 weeks following the last dose of study drugs.	
Number of Subjects (Planned and Analyzed): Planned: Approximately 100 subjects. Analyzed: 99 subjects were enrolled and received at least 1 dose of study drug.	

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria:

1. Male or female at least 18 years of age at time of screening.
2. US military veteran who was receiving healthcare through the VHA.
3. Chronic HCV infection prior to study enrollment. Chronic HCV infection was defined as 1 of the following:
 - Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before screening, and HCV RNA > 1,000 IU/mL at the time of screening; or
 - HCV RNA > 1,000 IU/mL at the time of screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrollment with evidence of chronic hepatitis C disease)
4. Screening laboratory result that indicated HCV GT1 infection.

Main Exclusion Criteria:

1. Women who were pregnant or breastfeeding.
2. Positive test result for hepatitis B surface antigen (HBsAg) or confirmed positive anti- human immunodeficiency virus (HIV) Ab test.
3. Use of (or prior use of) any investigational or commercially available anti-HCV agents other than interferon (IFN), pegylated interferon alfa-2a or alfa-2b (pegIFN), RBV, or sofosbuvir (including previous exposure to OBV, PTV, or DSV).
4. Clinically significant abnormalities or comorbidities that, in the opinion of the investigator, made the subject an unsuitable candidate for this study or its treatments. Subjects with active psychiatric conditions (depression, bipolar disorder, schizophrenia, anxiety, and/or post-traumatic stress disorder) were eligible if they were able to provide informed consent and adhere to the protocol requirements, including attending all scheduled study visits.
5. Presence of heavy alcohol use (> 5 drinks on the same occasion on each of 5 or more days in the past 30 days).
6. Any clinical evidence (or any past clinical evidence) of Child-Pugh B or C Classification (Child-Pugh Score \geq 7) or clinical history of liver decompensation such as ascites (noted on physical examination), variceal bleeding, or hepatic encephalopathy.
7. Confirmed presence of hepatocellular carcinoma (HCC) indicated on imaging techniques such as computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to screening or on an ultrasound performed at screening for subjects with cirrhosis (a positive ultrasound result was confirmed with CT scan or MRI).

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

Investigational Product	Manufacturer	Dosage Form/Mode of Administration	Bulk Lot Number
OBV/PTV/r	AbbVie	12.5/75/50 mg tablet/oral	13-005535
DSV	AbbVie	250 mg tablet/oral	14-004610
RBV	Kadmon or generic manufacturer	200 mg tablet/oral	14-005989

Duration of Treatment: Subjects received OBV/PTV/r + DSV ± RBV for 12 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 PT visits. Resistance: The following resistance information was provided for subjects who received study drugs who did not achieve SVR ₁₂ and who had a postbaseline sample with HCV RNA \geq 1000 IU/mL: 1) the variants at signature resistance-associated amino acid positions at baseline that were identified by population and/or deep sequencing and comparison to the appropriate prototypic reference sequence, 2) the amino acid variants in available postbaseline samples that were identified by population, deep, and/or clonal sequencing and comparison to the baseline sequence, 3) the amino acid variants in available postbaseline samples at signature resistance associated positions that were identified by population and/or deep sequencing and comparison to the appropriate prototypic reference sequence, and 4) the persistence of viral resistance. Safety: Safety and tolerability were assessed by monitoring adverse events, physical examinations, clinical laboratory tests, electrocardiogram (ECG), and vital signs.
Statistical Methods Efficacy: The primary endpoint was the percentage of subjects with SVR ₁₂ (HCV RNA < lower limit of quantification [LLOQ] 12 weeks after the last actual dose of study drugs). The number and percentage of subjects who achieved SVR ₁₂ was calculated with a 2-sided 95% confidence interval (CI) using the Wilson score method. The secondary efficacy endpoints were: <ul style="list-style-type: none">• 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 HCV RNA \geq LLOQ at the end of treatment);• The percentage of subjects with PT relapse (defined as confirmed HCV RNA \geq LLOQ between end of treatment and 12 weeks after the last dose of study drugs among subjects who completed treatment and with HCV RNA < LLOQ at the end of treatment);• The percentage of subjects who achieved SVR₁₂ among those with ongoing psychiatric comorbidities. The numbers and percentages of the subjects with virologic failure during treatment and with PT relapse were calculated with 2-sided 95% CIs using the Wilson score method.

Statistical Methods (Continued)

Resistance:

The following analyses were performed on the samples from subjects who did not achieve SVR₁₂ and had postbaseline resistance data available.

The HCV amino acid sequence as determined by next generation sequencing at the time of virologic failure or the sample closest in time after virologic failure with an HCV RNA level of ≥ 1000 IU/mL, and PT Week 24 time point was compared with the baseline and subtype-specific reference amino acid sequences. Listings by subject of all postbaseline variants at signature or non-signature amino acid positions detected by next generation sequencing relative to the baseline or reference amino acid sequences were provided for each direct-acting antiviral agent (DAA) target.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA[®]) (version 19.1). The number and percentage of subjects with treatment-emergent adverse events (TEAEs) were tabulated by primary System Organ Class (SOC) and preferred term. Tabulations were also provided in which the number of subjects with TEAEs was presented by severity rating and relationship to study drugs.

Changes from baseline in laboratory tests and vital sign measurements to each post-baseline visit were summarized descriptively. In addition, the number and percentage of subjects with post-baseline laboratory and vital sign values meeting prespecified criteria for potentially clinically significant (PCS) values, according to predefined criteria, during treatment were summarized.

Summary/Conclusions

Efficacy Results:

SVR₁₂ was achieved by 93/99 (93.9%) subjects (95% CI: 87.4%, 97.2%). One (1.0%) subject experienced on-treatment virologic failure and 2 (2.2%) subjects experienced post-treatment relapse by PT Week 12. SVR₁₂ rates were similar regardless of the presence of comorbidities such as cirrhosis, ongoing psychiatric disorders, and injection drug use.

Summary/Conclusions (Continued)	
Efficacy Results (Continued):	
Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR₁₂) (ITT Population)	
Virologic Finding	3-DAA ± RBV N = 99 n/N (%)
SVR₁₂	93/99 (93.9%) 95% CI^a: 87.4%, 97.2%
Reasons for nonresponse	
On-treatment virologic failure	1/99 (1.0)
Breakthrough	1/99 (1.0)
Fail to suppress	0/99
Relapse by Post-Treatment Week 12	2/90 (2.2)
Premature study drug discontinuation	3/99 (3.0)
HCV reinfection	0/99
Missing SVR ₁₂ data	0/99
Other	0/99
CI = confidence interval; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; ITT = intent-to-treat; RBV = ribavirin; SVR ₁₂ = sustained virologic response 12 weeks postdosing a. Calculated using the Wilson score method. Note: 3-DAA ± RBV = OBV/PTV/r 25/150/100 mg once daily (QD) + DSV 250 mg twice daily (BID) with or without RBV for 12 weeks or 24 weeks.	
Results for sustained virologic response 24 weeks postdosing (SVR ₂₄) were consistent with the primary efficacy results with 96.0% agreement between SVR ₁₂ and SVR ₂₄ . One (1.1%) subject experienced post-treatment relapse during the SVR ₂₄ window.	
Resistance Results:	
Resistance analyses based on next generation sequencing were conducted on 4 subjects who experienced virologic failure. Treatment-emergent substitutions D168H, D168V, D168Y, or Y56H and D168A/V were detected in NS3 in the 4 subjects. Two of the 4 subjects had Q30H and Y93H at baseline and at the time of failure in NS5A; treatment-emergent substitution M28T was detected in the other 2 subjects at the time of failure. Treatment-emergent substitutions M414T, S556G, or Y561H in NS5B were detected in 2 subjects.	

Summary/Conclusions (Continued)

Safety Results:

Treatment-emergent adverse events were mild or moderate in severity with the exception of events reported for 6 (6.1%) subjects who experienced severe adverse events.

The most common ($\geq 10.0\%$ of subjects) adverse events were fatigue, headache, nausea, insomnia, and pruritus.

Seven (7.1%) subjects experienced treatment-emergent serious adverse events (SAEs), 1 of whom experienced events that were assessed as having a reasonable possibility of being related to DAAs (mental status change due to drug interaction between DAAs and the antipsychotic quetiapine). No commonality was evident among the reported serious events. None of the SAEs resulted in study drug discontinuation.

Six (6.1%) subjects experienced at least 1 adverse event leading to premature discontinuation of study drugs, of which all had at least 1 DAA-related adverse event. None of the events were serious. Events of peripheral edema and peripheral swelling led to the premature discontinuation of study drug for 3 subjects, all at the same investigative site.

No subject died during the study.

No cases of hepatic decompensation or hepatic failure were identified. None of the subjects experienced a Grade 3 or higher alanine aminotransferase (ALT) elevation during the study and only 1 subject experienced a single Grade 3 total bilirubin elevation, which did not have an associated adverse event.

No clinically meaningful results of urinalysis, vital signs, or ECG were observed.

Conclusions:

- SVR₁₂ was achieved by 93.9% of subjects (95% CI: 87.4%, 97.2%) who received the OBV/PTV/r + DSV \pm RBV regimen for 12 or 24 weeks. The presence of ongoing psychiatric comorbidities had no impact on treatment efficacy.
- OBV/PTV/r + DSV \pm RBV demonstrated a favorable safety profile in US veterans with chronic HCV GT1 infection.