

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: Ombitasvir/Paritaprevir/Ritonavir, Dasabuvir		
Name of Active Ingredient: Ombitasvir/Paritaprevir/Ritonavir, Dasabuvir		
Title of Study: Open-label Study to Evaluate the Safety and Efficacy of the Combination of Ombitasvir, Paritaprevir/r ± Dasabuvir With or Without Ribavirin (RBV) in Adult Patients With GT1 or GT4 Chronic HCV Infection and Response to Prior Treatment of Early Stage Hepatocellular Carcinoma (GEODE – I)		
Investigator: Giuseppe (Joseph) Morelli, MD		
Rationale for Synoptic Clinical Study Report: Three subjects were enrolled in the study prior to the premature closure of study enrollment. The Sponsor decided to prematurely discontinue the enrollment of the study due to a significantly low rate of enrollment (target enrollment completion period changed from 6 months to 10 years). The main factors affecting enrollment were a significant increase in access to hepatitis C virus (HCV) treatment options in cirrhotic subjects, and changes in the treatment paradigm in the last year. All 3 subjects already enrolled in the study continued the study treatment and Post-Treatment periods according to the protocol.		
Study Sites: Multicenter (2 sites in the United States)		
Publications: None		
Studied Period (Years): First Subject First Visit: 27 July 2015 Last Subject Last Visit: 29 December 2016	Phase of Development: 3	
Objectives: The primary objectives of this study were to assess the safety and efficacy (the percentage of subjects achieving a 12-week sustained virologic response [SVR ₁₂ = HCV ribonucleic acid {RNA} < lower limit of quantification {LLOQ} 12 weeks after the last dose of the study drugs]) of coformulated ombitasvir/paritaprevir/ritonavir (OBV/PTV/r), with or without dasabuvir (DSV) coadministered with or without ribavirin (RBV) for 12 or 24 weeks in adult patients with documented complete response to prior treatment of early stage hepatocellular carcinoma (HCC) and either genotype (GT) 1 or 4 chronic HCV infection.		

Objectives (Continued):

The secondary objectives were to assess:

1. the percentage of subjects with virologic failure during treatment,
2. the percentage of subjects with relapse post-treatment,
3. the percentage of subjects with long term clinical outcomes from treatment through 24 weeks of follow-up, including de novo HCC lesions, liver decompensation, unexpected liver transplant, liver related death, or any of the above, and
4. the percentage of subjects with recurrent HCV infection post liver transplant out of all subjects with liver transplant during the study

Methodology:

This was a Phase 3, open-label, multi-center study evaluating the safety and efficacy of OBV/PTV/r ± DSV with or without RBV for 12 or 24 weeks in adults with GT1 or GT4 chronic HCV infection, compensated cirrhosis and documented complete response to treatment of early stage hepatocellular carcinoma.

Patients were planned to receive 12 or 24 weeks of OBV/PTV/r ± DSV with or without RBV based on HCV genotype and/or sub-genotype.

Patient Population	Treatment	Duration
Genotype 1b, with compensated cirrhosis	OBV/PTV/r 25/150/100 mg + DSV 250 mg BID	12 weeks
Genotype 1a, with compensated cirrhosis*	OBV/PTV/r 25/150/100 mg + DSV 250 mg BID + ribavirin	24 weeks
Genotype 4, with compensated cirrhosis	OBV/PTV/r 25/150/100 mg QD + ribavirin	24 weeks

* Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

Ribavirin was administered as weight-based 1000 or 1200 mg divided twice daily with the exception of subjects with a screening creatinine clearance (CrCL) < 50 mL/min. These subjects received alternating doses of RBV 200 mg and 400 mg.

The study consisted of 2 periods (not including a Screening period of up to 42 days), a Treatment Period (TP) and a Post-Treatment Period (PTP).

For all subjects who received at least 1 dose of study drug in the study, a 24 week PTP was planned to be followed after completion of treatment, or premature treatment discontinuation.

Safety and efficacy evaluations occurred throughout the study. The safety data was reviewed by the Sponsor, as this was an open-label study, during the Treatment Period of the study. Virologic failure criteria was evaluated and applied by the investigator.

Number of Subjects (Planned and Analyzed):

Approximately 60 subjects were planned to have been enrolled in the original protocol, based on the changing trends in health care landscape in this population during the past year, a significantly lower number of subjects were enrolled compared to that expected, and therefore the study enrollment was prematurely discontinued. Three subjects were enrolled in the study prior to the premature discontinuation of the study by the Sponsor based on a strategic business decision.

Diagnosis and Main Criteria for Inclusion:

Main Inclusion:

1. Male or female, at least 18 years of age at time of screening.
2. Chronic HCV infection prior to study enrollment. Chronic HCV infection was defined as one of the following:
 - Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for anti-HCV Ab 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 at or prior to enrollment.
3. Screening laboratory results indicated HCV genotype 1 or 4 infection.
4. HCC diagnosis according to European Association for the Study of the Liver (EASL)/American Association for the Study of Liver Diseases (AASLD) guidelines based on biopsy or imaging techniques obtained by 4-phase multidetector computed tomography scan or dynamic contrast-enhanced magnetic resonance imaging (MRI). Diagnosis should be based on the typical hallmark of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases).
5. Compensated cirrhosis defined as a Child-Pugh score of 5 or 6 at Screening.
 - A minimal rim of ascites if detected at imaging was acceptable. Excluded ascites that required the need to apply diuretic treatment to control ascites.
6. Early HCC defined as Barcelona Clinic Liver Cancer (BCLC) stage 0 or A. Note: If United Network for Organ Sharing/Milan criteria T1 – T2 was used to define early HCC, PI needed to identify the BCLC equivalent stage and report stage in case report form using BCLC criteria.
7. Subject received standard HCC treatment as recommended in EASL/AASLD guidelines or local guidelines. Some expected treatments were inclusive of, but not limited to, those listed in Section 5.3.1.1.
8. Documented complete response to early stage HCC treatment using the EASL-European Organisation For Research And Treatment of Cancer. Guidelines modified Response Evaluation Criteria in Solid Tumors criteria.
 - Complete response: Disappearance of any intratumoral arterial enhancement in all target lesions and non-target lesions.
 - If chemoembolization or radioembolization were the only interventions used to treat HCC, complete response was confirmed with MRI at Screening.

Diagnosis and Main Criteria for Inclusion (Continued):

Main Exclusion:

1. Use of known strong or moderate inducers of cytochrome P450 3A (CYP3A) in subjects receiving OBV/PTV/r with and without DSV, strong inducers and inhibitors (e.g., gemfibrozil) of cytochrome P450 2C8 (CYP2C8) in subjects receiving OBV/PTV/r with DSV, medications contraindicated for ritonavir or RBV (for those that receive RBV) and medications listed in the following table, within 2 weeks or 10 half-lives (if known), whichever is longer, prior to study drug administration, including but not limited to the medications listed below:

For medications contraindicated with AbbVie's 2-direct-acting antiviral agent (DAA) and 3-DAA regimen, refer to the recommended prescribing information section of the approved local product labels in countries where the regimen contained in this study (i.e., OBV/PTV/r, with and without DSV and/or RBV) has received marketing authorization. If locally approved labels are not available, refer to the following Contraindicated Medication list:

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

* Strong CYP2C8 inhibitors (e.g., gemfibrozil) and CYP2C8 inducers are not contraindicated with OBV/PTV/r (for GT4 subjects).

** When used for the treatment of pulmonary arterial hypertension.

Note: Not all medications contraindicated with ribavirin are listed above. Refer to the most current package inserts or product labeling of ribavirin for a complete list of contraindicated medications.

2. History of solid organ transplant, previous liver transplant, bone marrow transplant or malignant neoplastic disease.
3. Positive test result for hepatitis B surface antigen (HBsAg) or anti-human immunodeficiency virus antibody (HIV Ab).
4. Any current or past clinical evidence of Child-Pugh B or C Classification (Child-Pugh Score \geq 7).
5. Patients regardless of eligibility to liver transplant, who have a comorbid disease that might preclude completion of study follow-up.
6. Screening laboratory analyses showing any of the following abnormal laboratory results:
 - Creatinine Clearance (CrCl) < 30 mL/min as estimated by the Cockcroft-Gault equation:

$$\text{CrCl} = \frac{[(140 - \text{Age}) \times \text{Mass (in kg)} \times (0.85 \text{ if female})]}{[72 \times \text{Serum creatinine (in mg/dL)}]}$$
 - Albumin < 2.8 g/dL
 - Hemoglobin < 10 g/dL
 - Platelets < 25,000 cells per mm³
 - Total bilirubin > 3.0 mg/dL

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: OBV/PTV/r: 12.5/75/50 mg tablet/25/150/100 mg once daily (QD), Oral					
<table border="1"> <thead> <tr> <th>Study Drug</th> <th>Bulk Lot Number</th> </tr> </thead> <tbody> <tr> <td>OBV/PTV/r: 12.5/75/50 mg tablet</td> <td>15-001005</td> </tr> </tbody> </table>	Study Drug	Bulk Lot Number	OBV/PTV/r: 12.5/75/50 mg tablet	15-001005	
Study Drug	Bulk Lot Number				
OBV/PTV/r: 12.5/75/50 mg tablet	15-001005				
DSV: 250 mg tablet/250 mg twice daily (BID), Oral					
<table border="1"> <thead> <tr> <th>Study Drug</th> <th>Bulk Lot Number</th> </tr> </thead> <tbody> <tr> <td>DSV: 250 mg tablet</td> <td>15-000084</td> </tr> </tbody> </table>	Study Drug	Bulk Lot Number	DSV: 250 mg tablet	15-000084	
Study Drug	Bulk Lot Number				
DSV: 250 mg tablet	15-000084				
Ribavirin: 200 mg tablet/weight-based dosing 1000 or 1200 mg divided twice daily or adjusted for renal impairment subjects, Oral					
<table border="1"> <thead> <tr> <th>Study Drug</th> <th>Bulk Lot Number</th> </tr> </thead> <tbody> <tr> <td>Ribavirin 200 mg tablet</td> <td>14-003370</td> </tr> </tbody> </table>	Study Drug	Bulk Lot Number	Ribavirin 200 mg tablet	14-003370	
Study Drug	Bulk Lot Number				
Ribavirin 200 mg tablet	14-003370				
Duration of Treatment: Subjects received OBV/PTV/r ± DSV with or without RBV for 12 or 24 weeks according to HCV GT and sub genotype.					
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Not applicable.					
Criteria for Evaluation					
Efficacy: <ul style="list-style-type: none"> Plasma HCV RNA (IU/mL) was to be assessed during the treatment and post-treatment treatment periods. Clinical outcomes were to be evaluated from treatment through 24 weeks of follow-up: de novo HCC lesions, liver decompensation, unexpected liver transplant, liver related death. The percentage of subjects with recurrent HCV infection, post liver transplant out of all subjects with liver transplant during the study was to be assessed. 					
Resistance: The following resistance information was to be assessed for subjects who experience virologic failure: the variants at each amino acid position at baseline identified by deep sequencing relative to the appropriate prototypic reference sequence, and the variants at the available post-baseline time points identified by deep sequencing relative to baseline and to the appropriate prototypic reference sequences.					
Safety: Safety and tolerability were to be 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 secondary endpoints were:

1. the percentage of subjects with virologic failure during treatment,
2. the percentage of subjects with relapse post-treatment,
3. the long term clinical outcomes of interest from treatment through 24 weeks of follow-up defined as: de novo HCC lesions, liver decompensation, unexpected liver transplant, liver related death, or any of the above, and
4. the percentage of subjects with recurrent HCV infection post liver transplant out of all subjects with liver transplant during the study.

For the primary and secondary endpoints, the simple percentage of subjects in study treatment meeting the endpoint was to be presented.

Resistance:

The following resistance information was to be summarized for the subset of subjects who experience virologic failure:

1. the amino acid variants at signature resistance-associated positions at baseline identified by deep sequencing relative to the appropriate prototypic reference sequence,
2. the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by deep sequencing relative to the baseline sequence, and
3. the amino acid variants in available post-baseline samples at signature resistance associated positions identified by deep sequencing relative to the appropriate prototypic reference sequence.

Safety:

The overall number and percentage of subjects reporting treatment-emergent adverse events was to be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Tabulations were also to be 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 was to be summarized. Laboratory test and vital sign values that were potentially clinically significant, according to predefined criteria, were to be identified and the number and percentage of subjects with potentially clinically significant values was to be calculated.

Summary/Conclusions

The study enrollment was discontinued prematurely by the Sponsor due to a significantly low rate of enrollment (target enrollment completion period changed from 6 months to 10 years). Three GT1a HCV subjects were enrolled in the study before study enrollment was discontinued. All 3 subjects continued the study treatment and Post Treatment periods according to the protocol.

Efficacy Results:

All 3 subjects achieved sustained virologic response at 4, 12, and 24 weeks post-treatment. No subject experienced on-treatment virologic failure or post-treatment relapse during the study.

Summary/Conclusions (Continued)

Resistance Results:

Since no subjects experienced virologic failure, no resistance testing was conducted.

Safety Results:

Three subjects were enrolled in the study and received ombitasvir/paritaprevir/ritonavir, dasabuvir and ribavirin for 24 weeks and completed the 24 week PTP. All subjects were included in the safety analyses (N = 3).

All 3 subjects experienced at least 1 TEAE, 2 subjects had events assessed as having a reasonable possibility of being related to DAAs. No subjects experienced death, an SAE, an adverse event leading to discontinuation, or Grade 3 or higher hemoglobin or liver function test values during the study. One subject experienced Grade 1 leukopenia, lymphopenia, and neutropenia adverse events which resolved with no change to study drug or concomitant medications. No clinically significant laboratory measurements for other laboratory parameters or for vital sign parameters were observed. No subjects experienced any Clinical Outcomes of liver-related death, unexpected liver transplantation, liver decompensation and/or de novo or recurrence of HCC lesions.

Conclusions:

No conclusions can be drawn from the limited data obtained from this study.