

## 2.0 Synopsis

<b>AbbVie Inc.</b>	<b>Individual Study Table Referring to Part of Dossier:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Ombitasvir, paritaprevir, ritonavir, dasabuvir	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Ombitasvir, paritaprevir, ritonavir, dasabuvir	<b>Page:</b>	
<b>Title of Study:</b> An Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with Low-Dose Ribavirin QD in Subjects with Genotype 1a Chronic Hepatitis C Virus Infection (GEODE II)		
<b>Coordinating Investigator:</b> Fred Poordad, MD		
<b>Study Sites:</b> 10 sites in the United States		
<b>Publications:</b> 1 abstract		
<b>Studied Period (Years):</b> First Subject First Visit: 28 October 2015 Last Subject Last Visit: 28 December 2016	<b>Phase of Development:</b> 3	
<b>Objectives:</b> To assess safety and to compare the efficacy (the percentage of subjects achieving sustained virologic response (SVR) 12 weeks [SVR <sub>12</sub> ] after the last dose of study drug) of treatment with ombitasvir/paritaprevir/ritonavir and dasabuvir with fixed dose ribavirin 600 mg once daily (QD) in genotype 1a (GT1a) non-cirrhotic infected adult subjects who are either hepatitis C virus (HCV) treatment-naïve or treatment-experienced with interferon or pegylated interferon with or without ribavirin against the historical SVR <sub>12</sub> rate for ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) and dasabuvir (DSV) with weight based (1000 mg to 1200 mg daily) ribavirin (RBV).		
<b>Methodology:</b> This was a Phase 3 open-label, single arm, multicenter study. A total of 105 subjects received OBV/PTV/r 25/150/100 mg once daily (QD) and DSV 250 mg twice daily (BID) with ribavirin 600 mg QD for up to 12 weeks. Study treatment duration could have been extended for up to 24 weeks in some subjects if the efficacy treatment adjustment (futility) criteria had been met. The duration of the study was up to 36 weeks (not including the screening period), and consisted of 2 periods: the 12 week Treatment Period and the 24-week Post-Treatment Period. In the Post Treatment Period, all subjects administered at least 1 dose of study drug were to be followed for 24 weeks to monitor for safety, HCV (hepatitis C virus) RNA (ribonucleic acid) rebound, and the emergence and/or persistence of resistant viral variants.		

**Methodology (Continued):**

For the first 20 subjects completing treatment, the Sponsor assessed the overall virologic failure rate to see if the rate exceeded 5%, and examined the subjects with virologic failure to determine if all subjects needed to receive full dose, weight-based RBV for 12 additional weeks or only a subset or if enrollment needed to be paused. An interim analysis occurred after all subjects reached Post-Treatment Week 12, or prematurely discontinued the study.

The primary efficacy endpoint was the number and percentage of intent-to-treat (ITT) subjects with SVR<sub>12</sub> (HCV RNA < lower limit of quantification (LLOQ) 12 weeks after the last actual dose of study drugs). The primary analysis occurred after all subjects completed the Post-Treatment Week 12 Visit or prematurely discontinued study to assess the percentage of subjects achieving SVR<sub>12</sub>. The final analysis was conducted when all subjects completed the Post-Treatment Week 24 Visit or prematurely discontinued from the study.

**Number of Subjects (Planned and Analyzed):**

Approximately 100 subjects were planned; 105 subjects were enrolled and received at least 1 dose of study drug.

**Diagnosis and Main Criteria for Inclusion/Exclusion:**

Subjects (at least 18 years of age at time of Screening) had chronic HCV infection prior to study enrollment defined as 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 positive for anti-HCV Ab and 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), with screening laboratory result indicating HCV GT1a infection, HCV treatment-naïve or if treated previously, only with interferon (IFN) or pegylated interferon (pegINF) with or without RBV.

Only non-cirrhotic subjects could be enrolled as determined by local standard practice, with documented results of one of the following: liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, or a FibroScan performed within 6 months prior to or during screening with a score of < 12.5 kiloPascals; or a screening Fibrotest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2. Subjects with a positive test result for hepatitis B surface antigen (HBsAg) or anti-human immunodeficiency virus antibody (HIV Ab), HCV genotype performed during screening indicated presence of any subtype other than 1a, or unable to subtype, prior or current use of any investigational or commercially available anti-HCV agents other than IFN, pegINF or RBV, or women who were pregnant or breastfeeding, were excluded.

<b>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</b>					
<b>Investigational Product</b>	<b>Manufacturer</b>	<b>Mode of Administration</b>	<b>Dosage Form</b>	<b>Strength</b>	<b>Bulk Lot Number</b>
Ombitasvir/paritaprevir/ritonavir	AbbVie	Oral	Tablet	12.5 mg/ 75 mg/ 50 mg	14-005707
Dasabuvir	AbbVie	Oral	Tablet	250 mg	15-000083, 14-005917
Ribavirin	Kadmon Pharmaceuticals	Oral	Tablet	600 mg <sup>a</sup>	15-005344
Ribavirin for dose adjustment <sup>a</sup>	DSM Pharmaceuticals for Kadmon	Oral	Tablet	200 mg	14-005989
<p>a. Ribavirin dose was decreased for toxicity management purposes or in the event of deterioration of an underlying chronic renal insufficiency. Ribavirin dose was increased if subject met efficacy treatment adjustment (futility) criterion.</p>					
<b>Duration of Treatment:</b>					
Subjects received ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD and dasabuvir 250 mg BID with ribavirin 600 mg QD for up to 12 weeks (up to 24 weeks, based on subject meeting efficacy treatment adjustment criterion).					
<b>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</b>					
Not applicable.					
<b>Criteria for Evaluation</b>					
<b>Efficacy:</b>					
Virologic response was assessed by HCV RNA in IU/mL and was evaluated at all Treatment Period Visits and at all Post-Treatment Period Visits (through 24 weeks after completion of treatment).					
<b>Resistance:</b>					
The following information was tabulated and summarized: 1) for all subjects, the variants at baseline at signature resistance-associated amino acid positions relative to the appropriate prototypic reference sequence; 2) for subjects receiving active drugs who do not achieve SVR <sub>12</sub> : post-baseline variants at each amino acid position relative to baseline; and 3) post-baseline variants at signature amino acid position relative the appropriate prototypic reference sequence.					
<b>Patient-Reported Outcomes (PROs):</b>					
Health State Utility was measured using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L) Questionnaire.					
<b>Pharmacokinetic:</b>					
Plasma samples for ombitasvir, paritaprevir, ritonavir, dasabuvir, dasabuvir M1 metabolite, and ribavirin were to be collected at each study visit (beginning at Week 2) from each subject up to completion of the treatment (12 weeks).					

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**Criteria for Evaluation (Continued)**

**Safety:**

The following safety evaluations were to be performed during the study: adverse event (AE) monitoring, vital signs, physical examination, 12-lead electrocardiograms, and laboratory test assessments.

**Statistical Methods**

**Efficacy:**

The ITT population was defined as all enrolled subjects who received at least 1 dose of study drug. The primary analyses were performed on the ITT population and sensitivity analyses were done on the modified intent-to-treat genotype and virologic failure (mITT-GT-VF) population, defined as all subjects in the ITT population excluding subjects who did not have HCV genotype 1a infection and subjects who did not achieve SVR<sub>12</sub> but were not categorized as virologic failures (i.e., on treatment virologic failures or relapse<sub>12</sub>).

The primary efficacy endpoint was number and percentage of subjects in the ITT population with SVR<sub>12</sub> (HCV RNA < LLOQ 12 weeks after the last actual dose of study drugs). The number and percentage of subjects with SVR<sub>12</sub> were to be summarized along with a 2-sided 95% confidence interval using the normal approximation to the binomial distribution. Non-inferiority of ombitasvir/paritaprevir/ritonavir and dasabuvir (3-DAA + low dose RBV (600 mg) against 3-DAA + weight-based RBV (1000 to 1200 mg) was achieved if the lower bound of the confidence interval was above 92%.

- The percentage of subjects with on-treatment virologic failure (breakthrough defined as confirmed HCV RNA  $\geq$  LLOQ after HCV RNA < LLOQ during treatment or confirmed increase of at least 1 log<sub>10</sub> IU/mL from nadir at any time point during treatment, or failure to suppress during treatment [all on treatment values of HCV RNA  $\geq$  LLOQ] with at least 6 weeks [defined as active study drug duration  $\geq$  36 days] of treatment);
- The percentage of subjects with post-treatment relapse, defined as confirmed HCV RNA  $\geq$  LLOQ between end of treatment and 12 weeks after last dose of study drug (up to and including the SVR<sub>12</sub> assessment time point), excluding re-infection, among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment.

The primary safety endpoint was the proportion of subjects with hemoglobin < 10 g/dL during the course of 3D + low dose RBV (600 mg QD) treatment and hemoglobin decreased from baseline.

**Resistance:**

For all subjects that received study drugs, the variants at signature amino acid positions at baseline identified by population relative to the appropriate prototypic reference sequence were analyzed.

The following resistance information was analyzed for subjects receiving active drugs who did not achieve SVR (and who have baseline and post-baseline samples with HCV RNA  $\geq$  1000 IU/mL): 1) the variants at available post-baseline time points identified by population or next generation sequencing relative to the baseline sequence; 2) the variants at signature amino acid positions in available post-baseline time points identified by population or next-generation sequencing relative to the appropriate reference sequence; 3) the amino acid variants that emerge in isolates from at least 2 subjects were summarized, and 4) the persistence of treatment-emergent variants were summarized.

**PROs:**

Summary statistics of value and change from baseline to treatment and post-treatment visits were provided for EQ-5D-5L health index and visual analog scale (VAS) scores.

### **Statistical Methods (Continued)**

#### **Pharmacokinetic:**

Plasma concentrations were summarized for paritaprevir, ritonavir, ombitasvir, dasabuvir, dasabuvir M1 metabolite and ribavirin using the data from all subjects.

#### **Safety:**

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

The number and percentage of subjects with treatment-emergent AEs (i.e., any event that began or worsened in severity after initiation of study drug through 30 days after the last dose of study drug) were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) primary System Organ Class (SOC) and preferred term (PT). The tabulation of the number of subjects with treatment-emergent AEs was also provided by severity rating and relationship to study drug.

Laboratory data values 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 in clinical laboratory values from low/normal to high and high/normal to low based on the normal range were summarized.

In addition, the number and percentage of subjects with post-baseline laboratory or vital sign values meeting pre-specified criteria for potentially clinically significant (PCS) laboratory values were summarized.

### **Summary/Conclusions**

#### **Efficacy Results:**

The primary efficacy endpoint was the percentage of subjects with SVR<sub>12</sub> (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) and was achieved in 89.5% (CI 95%: 83.7, 95.4) of non-cirrhotic GT1a-infected subjects intended to be treated with OBV/PTV/r + DSV + low dose RBV (600 mg per day) for 12 weeks. As the pre-specified lower bound of the 2-sided 95% confidence interval to achieve non-inferiority was set at 92%, this implies that the study did not achieve non-inferiority versus 3-DAA + full dose RBV, the prevailing standard-of-care treatment regimen at the time of this study's initiation.

The sensitivity analysis for the mITT-GT-VF population resulted in an SVR<sub>12</sub> rate of 94.9% (CI 95%: 90.6, 99.3) with 94 of 99 subjects.

At Week 4, 102 (97.1%) subjects responded with rapid virological response (RVR) (HCV RNA < LLOQ) and 101 subjects (96.2%) showed end of treatment response (EOTR). Most subjects (≥ 98%) had HCV RNA < LLOQ at Weeks 4, 8, 12, and the final treatment visit, based on subjects observed at the respective visit. Most subjects also responded with RVR, EOTR, 4-week sustained virologic response (SVR<sub>4</sub>), SVR<sub>12</sub>, or 24-week sustained virologic response (SVR<sub>24</sub>), but with response decreasing from RVR (97.1%) to SVR<sub>24</sub> (84.8%).

Concordance analysis of subjects responding with SVR<sub>12</sub> and SVR<sub>24</sub> (HCV RNA < LLOQ) resulted in a 95.2% agreement.

One subject (1%) experienced a breakthrough and 4 among 97 subjects completing treatment and with EOTR experienced post-treatment relapse (4.1%). No subjects failed to suppress HCV RNA during the Treatment Period and no subjects were re-infected with HCV.

### **Summary/Conclusions (Continued)**

#### **Resistance Results:**

The prevalence of NS3 Q80K and OBV-specific baseline polymorphisms among the GT1a-infected subjects was 46.5% (46/99) and 11.5% (11/96), respectively. PTV- and DSV-specific baseline polymorphisms were rare and had no impact on SVR<sub>12</sub>. NS3 Q80K or OBV-specific baseline polymorphisms alone in the absence of polymorphisms in another target had no impact on SVR<sub>12</sub>, while a combination of these polymorphisms was associated with lower SVR<sub>12</sub> rates. The SVR<sub>12</sub> rate in subjects with NS3-Q80K in combination with OBV-specific polymorphisms in NS5A was 57.1% (4/7). The SVR<sub>12</sub> rates with OBV-specific baseline polymorphisms alone (100%, 4/4) or NS3-Q80K alone (94.7%, 36/38), were not significantly different from the overall SVR<sub>12</sub> rate (94.8%, 91/96), or the rate in subjects without either OBV-specific polymorphisms or NS3-Q80K (100%, 47/47).

Among the 6 subjects who experienced virologic failure, treatment-emergent substitutions D168A/V with or without Y56H or Q80K + S122N in NS3 were detected in 3 subjects, M28T or Q30R in NS5A were detected in 3 subjects, and C316Y, S556G, or A553T in NS5B were detected in 4 subjects.

#### **Patient Reported Outcome Results**

Analysis of the change from Baseline by visit for the EQ-5D VAS score showed a mean increase through Post-Treatment Week 12, when the highest mean increase was seen (6.0 standard deviation [SD] 11.80), followed by a slight decrease Post-Treatment Week 24 (4.6 SD 13.48). The mean increase from baseline to the final post-treatment visit was 5.0 (SD 13.40). Analysis of the change from Baseline by visit for the EQ-5D-5L health index score showed a modest mean increase from Post-Treatment Week 4 through the final post-treatment visit. Mean increase was 0.02 at Post-Treatment Week 4, 12, and the final post-treatment visit. A slight decrease was seen at Post-Treatment Week 24 (0.01 SD 0.122). None of the changes observed in the EQ-5D-5L were considered clinically meaningful.

#### **Pharmacokinetic Results:**

When compared with earlier studies with 3-DAA regimen + weight-based full dose ribavirin, the present study of 3-DAA regimen + low dose ribavirin had comparable exposures of direct-acting antiviral agents (DAAs) and ritonavir, while the ribavirin exposures were approximately 50% lower.

#### **Safety Results:**

Ombitasvir/paritaprevir/ritonavir and dasabuvir with low-dose ribavirin for 12 weeks was generally well tolerated. The majority (73.3%) of subjects experienced at least 1 treatment-emergent AE, most of which were mild (40/77 subjects) in severity. The most common events reported ( $\geq 10\%$  of subjects) were fatigue (27.6%), headache (13.3%), insomnia (11.4%), and nausea (10.5%), most of which were assessed by the investigator as having a reasonable possibility of being treatment-related to either DAAs or RBV. None of these events were severe.

Severe treatment emergent adverse events (TEAEs) were limited to cyclic vomiting syndrome (grade 4), sciatica (grade 3), and psychotic disorder (grade 4) that occurred in 1 subject (1.0%) each. Of these, cyclic vomiting syndrome and psychotic disorder were assessed as serious; psychotic disorder led to premature discontinuation of study drug. One (1.0%) additional subject experienced bipolar I disorder (grade 4), which was also assessed as serious, although moderate in severity and without impact on study drug.

**Summary/Conclusions (Continued)**

**Safety Results (Continued):**

No deaths were reported during the study. Serious AEs were infrequent (3/105 subjects [2.9%]; bipolar I disorder, psychotic episode, and cyclic vomiting syndrome); the SAEs were assessed as unrelated to treatment, except for bipolar I disorder, which was assessed as having a reasonable possibility of being related to both DAA and RBV treatment.

The maximum mean decrease in hemoglobin value from baseline was -12.4 at Week 12, and only 1 subject experienced a grade 2 hemoglobin value. Two subjects had their RBV dose reduced due to decreased hemoglobin values.

Hemoglobin decreases, alanine aminotransferase (ALT) increase, and aspartate aminotransferase (AST) increase, were reported less frequently than in studies of similar populations treated with full dose RBV. No subject met the criteria for Hy's law.

The safety profile of the current study is consistent with the safety profile observed in the 3-DAA pivotal studies, with most AEs of mild to moderate severity and 1.9% of subjects discontinuing study drug due to AEs.

**Conclusions:**

Treatment with a 12-week regimen of 3-DAA coadministered with low dose RBV resulted in a primary SVR<sub>12</sub> rate of 89.5% (95% CI: 83.7%, 95.4%) in GT1a-infected, treatment-naïve or experienced with IFN or pegIFN ± RBV HCV subjects without cirrhosis. As the pre-specified lower bound of the 2-sided 95% confidence interval to achieve non-inferiority was set at 92%, this implies that the study did not achieve non-inferiority vs. the historical control of 3-DAA + full dose RBV, the prevailing standard-of-care treatment regimen at the time of this study's initiation.

3-DAA regimen coadministered with low dose (600 mg) RBV was generally safe and well tolerated in GT1a-infected subjects. Adverse events reported in this study were generally consistent with the established safety profile for RBV and those demonstrated for these DAAs and the combination of these DAAs with RBV in previous studies of subjects with and without cirrhosis.