

## 2.0 Synopsis

<p><b>AbbVie Inc.</b></p>	<p><b>Individual Study Table Referring to Part of Dossier:</b></p>	<p><b>(For National Authority Use Only)</b></p>
<p><b>Name of Study Drug:</b> Ombitasvir/ABT-450/ritonavir; dasabuvir</p>	<p><b>Volume:</b></p> <p><b>Page:</b></p>	
<p><b>Name of Active Ingredient:</b></p> <p><u>Ombitasvir:</u> Dimethyl ([(2<i>S</i>,5<i>S</i>)-1-(4-<i>tert</i>-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2<i>S</i>)pyrrolidine-2,1-diyl}[(2<i>S</i>)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate</p> <p><u>ABT-450 (paritaprevir):</u> (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>,14,15,16,16<i>a</i>-tetradecahydrocyclopropa[<i>e</i>]pyrrolo[1,2-<i>a</i>][1,4]diazacyclopentadecine-14<i>a</i>(5<i>H</i>)-carboxamide hydrate</p> <p><u>ritonavir (r):</u> [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</p> <p><u>dasabuvir:</u> 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)</p>		

<b>Title of Study:</b> An Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir and Dasabuvir in Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-III)	
<b>Coordinating Investigator:</b> Jordan Feld, MD	
<b>Study Sites:</b> 19 investigative sites in the United States, Canada, and Belgium.	
<b>Publications:</b> 2 abstracts	
<b>Studied Period (Years):</b> First Subject First Visit: 15 September 2014 Last Subject Last Visit: 01 September 2015	<b>Phase of Development:</b> 3b
<b>Objectives:</b> The primary objectives of this study were to compare the efficacy (the percentage of subjects achieving a 12-week sustained virologic response, SVR <sub>12</sub> [HCV RNA < lower limit of quantification {LLOQ} 12 weeks following treatment]) of co-formulated ombitasvir/paritaprevir/r and dasabuvir administered for 12 weeks to the historical SVR <sub>12</sub> rate of sofosbuvir plus pegylated interferon (pegIFN)/ribavirin (RBV) and to assess the safety of the direct-acting antiviral agent (DAA) combination regimen in HCV genotype 1b (GT1b)-infected adult subjects with compensated cirrhosis. The secondary objectives of this study were to assess the number and percentage of subjects with virologic failure during treatment and the percentage of subjects with virologic relapse.	
<b>Methodology:</b> This was a Phase 3b, open-label, single-arm, multicenter study evaluating the efficacy and safety of ombitasvir/paritaprevir/r and dasabuvir administered for 12 weeks in HCV GT1b-infected, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis. The duration of the study was up to 36 weeks (not including a screening period of up to 42 days) and consisted of a 12-week Treatment Period and a 24-week Post-Treatment Period for all subjects who received study drugs. All subjects who received at least 1 dose of study drug were followed for 24 weeks post-treatment to monitor for safety, HCV RNA, and the emergence and persistence of resistant viral variants and assessment of Patient-Reported Outcome (PRO) instruments. The primary analysis occurred after all subjects had completed through Post-Treatment Week 12 or prematurely discontinued the study. All remaining data through Post-Treatment Week 24 were summarized in the end-of-study analysis.	
<b>Number of Subjects (Planned and Analyzed):</b> Approximately 60 subjects were planned; 60 subjects were enrolled and received at least 1 dose of study drug.	

<b>Diagnosis and Main Criteria for Inclusion:</b>					
Subjects were HCV GT1b-infected, treatment-naïve or previous pegIFN/RBV treatment-experienced adults (at least 18 years of age) with compensated cirrhosis. 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 must have been surgically sterile, had male partners only, or agreed to practice 2 effective methods of birth control throughout the course of the study. Subjects had a chronic HCV GT1b infection, a plasma HCV RNA > 1,000 IU/mL, and documentation of cirrhosis (e.g., a Metavir score > 3 or an Ishak score > 4) or FibroScan® result ≥ 12.5 kPa.					
<b>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</b>					
Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
Ombitasvir/paritaprevir/r	AbbVie	Oral	Tablet	12.5 mg/75 mg/50 mg	13-001960
Dasabuvir	AbbVie	Oral	Tablet	250 mg	12-007842
<b>Duration of Treatment:</b> Subjects received ombitasvir/paritaprevir/r 25/150/100 mg once daily (QD) and dasabuvir 250 mg twice daily (BID) for 12 weeks.					
<b>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</b> Not applicable.					
<b>Criteria for Evaluation</b>					
<b>Efficacy:</b> HCV RNA in IU/mL was assessed at all Treatment Period visits and at all Post-Treatment visits.					
<b>Resistance:</b> No subject demonstrated virologic failure and no resistance testing was conducted.					
<b>Patient-Reported Outcomes:</b> The change in disease-specific function and wellbeing were assessed using the Patient-Reported Outcome (PRO) instruments. Health State Utility was measured using the EuroQol-5 Dimensions 5 Level (EQ-5D-5L) instrument. General Health Related Quality of Life (HRQoL) was assessed using the Short Form 36, version 2 (SF-36v2) non-disease specific HRQoL instrument. Fatigue was measured using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) instrument.					
<b>Pharmacokinetic:</b> Plasma concentrations of paritaprevir, ritonavir, ombitasvir, dasabuvir, and dasabuvir M1 metabolite were determined.					
<b>Safety:</b> Safety and tolerability were assessed by monitoring adverse events, physical examinations, clinical laboratory tests, 12-lead electrocardiograms, and vital signs.					

## **Statistical Methods**

### **Efficacy:**

The first primary efficacy endpoint was non-inferiority for the 3-DAA regimen in SVR<sub>12</sub> (HCV RNA < LLOQ 12 weeks after the last actual dose of study drugs) to a historical threshold for sofosbuvir plus pegIFN/RBV for the treatment of subjects with HCV GT1b infection and cirrhosis using a 2-sided 95% confidence interval from Wilson's score method. Non-inferiority was to be declared if the lower confidence bound was greater than 72.7%.

The second primary efficacy endpoint was superiority for the 3-DAA regimen in SVR<sub>12</sub> to a historical threshold for sofosbuvir plus pegIFN/RBV for the treatment of subjects with HCV GT1b infection and cirrhosis using a 2-sided 95% confidence interval from Wilson's score method. Superiority was to be declared if the lower confidence bound was greater than 83.2%.

In order to control the Type I error rate at 0.05, a fixed-sequence testing procedure was used for the primary efficacy endpoints. Only if success had been demonstrated for the first primary efficacy endpoint of non-inferiority would the testing continue to the second primary efficacy endpoint of superiority of the SVR<sub>12</sub> rate for the 3-DAA regimen to the historical SVR<sub>12</sub> rate for sofosbuvir plus pegIFN/RBV.

The secondary efficacy endpoints were: the percentage of subjects with on-treatment virologic failure (breakthrough defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, or confirmed increase from nadir in HCV RNA [2 consecutive HCV RNA measurements > 1 log<sub>10</sub> IU/mL above nadir] at any time point during treatment, or failure to suppress during treatment [all on-treatment values of HCV RNA ≥ LLOQ] with at least 6 weeks [defined as active study drug duration – 36 days] of treatment) and the percentage of subjects with post-treatment relapse (relapse<sub>12</sub> defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of active study drug [up to and including the SVR<sub>12</sub> assessment time point] for a subject with HCV RNA < LLOQ at Final Treatment Visit who completes treatment. Completion of treatment was defined as a study drug duration – 77 days).

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.

### **Patient-Reported Outcomes:**

Exploratory analyses of the change in disease-specific function and wellbeing were assessed using the Patient-Reported Outcome (PRO) instruments. Health State Utility was measured using the EuroQoL-5 Dimensions 5 Level (EQ-5D-5L) instrument. General Health Related Quality of Life (HRQoL) was assessed using the Short Form 36, version 2 (SF-36v2) non-disease specific HRQoL instrument. Fatigue was measured using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) instrument. The EQ-5D-5L was analyzed by utility score and by visual analogue scale (VAS) response. Change from baseline in the PRO summary measures was assessed. The minimally important difference (MID) for the SF-36v2 was a decrease of 5 points from baseline to the Final Treatment Visit for both the Mental Component Summary and Physical Component Summary scores. The percentage of subjects with a change from baseline to the Final Treatment Visit in the Mental Component Summary and Physical Component Summary scores greater than the appropriate MID was calculated.

**Statistical Methods (Continued)**

**Pharmacokinetic:**

Individual plasma concentrations for paritaprevir, ritonavir, ombitasvir, dasabuvir, and dasabuvir M1 metabolite were tabulated and summarized. Summary statistics were computed based on plasma concentrations by binned time interval since last dose.

**Safety:**

The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by 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:**

Sustained virologic response 12 and 24 weeks postdosing was achieved by all 60 (100%) subjects. A 12-week treatment with 3-DAA regimen (without RBV) was noninferior and superior to the historical SVR<sub>12</sub> rate for sofosbuvir plus pegIFN/RBV therapy for 12 weeks.

**Resistance Results:**

No subject demonstrated virologic failure, and resistance testing was therefore not conducted.

**Patient-Reported Outcome Results:**

The majority of subjects who were treated with the 3-DAA regimen did not experience decreases from baseline in their HRQoL, function, and wellbeing (per SF-36v2 Mental Component Summary and Physical Component Summary scores) at the end of treatment that met criteria to be considered of minimal importance, including subjects who experienced increases from baseline at end of treatment. Improvement over the baseline in the group mean was observed in all PRO measurements at both the end of treatment and the Final Post-Treatment Visit.

**Pharmacokinetic Results:**

The observed geometric mean C<sub>trough</sub> concentrations of ritonavir, dasabuvir, dasabuvir M1, and ombitasvir in pegIFN/RBV treatment-naïve and treatment-experienced HCV GT1b-infected adults with compensated cirrhosis in the current study were comparable to the exposures observed in HCV genotype 1-infected adults with compensated cirrhosis in Study M13-099. The geometric mean paritaprevir trough concentrations from GT1b-infected subjects with compensated cirrhosis in the current study were approximately 61% higher compared to those from HCV genotype 1-infected adults with compensated cirrhosis from a previous study, however, the range of paritaprevir exposures were comparable. Since ribavirin is not expected to interfere in elimination pathways of paritaprevir, the higher observed geometric mean C<sub>trough</sub> values of paritaprevir observed in this study compared to a previous study could be due to the relatively small number of samples in the time interval that was considered for C<sub>trough</sub> and high variability (> 100% CV).

**Summary/Conclusions (Continued)**

**Safety Results:**

Ombitasvir/paritaprevir/r and dasabuvir for 12 weeks in HCV GT1b, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis was generally well tolerated with no subjects prematurely discontinuing study drug because of a treatment-emergent adverse event.

The majority of subjects (76.7%) experienced 1 or more treatment-emergent adverse event during the Treatment Period, and most were mild or moderate in severity.

The overall incidence of treatment-emergent serious adverse events was low (1.7%). There were no treatment emergent adverse events that led to premature discontinuation of study drug. No deaths were reported. No subject experienced an event of hepatic decompensation in this study.

Treatment-emergent adverse events reported for 10.0% of subjects were fatigue, diarrhea, headache, arthralgia, dizziness, insomnia, and pruritus.

Clinically significant lab abnormalities were infrequent and occurred at a lower frequency than previously observed among GT1 cirrhotic subjects who received the current label recommended 3-DAA regimen with RBV for the same 12-week duration.

**Conclusions:**

Treatment with a 12-week regimen of ombitasvir/paritaprevir/r and dasabuvir resulted in an SVR<sub>12</sub> rate of 100%, which demonstrated both noninferiority and superiority to the historical control rate for sofosbuvir plus pegIFN/RBV therapy for 12 weeks in HCV GT1b-infected subjects with compensated cirrhosis, either treatment-naïve or pegIFN/RBV-experienced. Treatment was well tolerated with a low rate of serious adverse events and lab abnormalities. Based on a cross-study comparison in a similar patient population from Study M13-099, the rates of common adverse events, anemia and hyperbilirubinemia, were numerically lower in this study without RBV than was observed in Study M13-099 where RBV was given. These data suggest that a 12-week course of ombitasvir/paritaprevir/r and dasabuvir without RBV is an appropriate treatment recommendation in this population.