

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
<p>Name of Study Drug: ombitasvir, paritaprevir (ABT-450), ritonavir, dasabuvir, ribavirin</p>	<p>Volume:</p>	
<p>Name of Active Ingredient:</p> <p>ombitasvir (ABT-267): 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 (ABT-450): (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[e]pyrrolo[1,2-<i>a</i>][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate</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 (ABT-333): 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>	<p>Page:</p>	
<p>Title of Study: An Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ombitasvir/ABT-450/Ritonavir and Dasabuvir With or Without Ribavirin (RBV) in Treatment-Naïve or Treatment-Experienced Adults in Brazil with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (TOPAZ III)</p>		

Coordinating Investigator: Ana de Lourdes Candolo Martinelli, MD	
Study Sites: 16 sites in Brazil	
Publications: 1 (abstract)	
Studied Period (Years): First Subject First Visit: 27 April 2015 Last Subject Last Visit: 26 September 2016	Phase of Development: 3b
<p>Objectives:</p> <p>The primary objectives of this study were to evaluate the efficacy (the proportion of subjects achieving SVR₁₂ defined as HCV ribonucleic acid (RNA) < lower limit of quantification [LLOQ] 12 weeks following treatment) and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin (RBV), in adults in Brazil with genotype (GT) 1 chronic HCV infection.</p> <p>The secondary objectives were: to calculate the SVR₁₂ rates by fibrosis stage (F3 and F4), prior type of treatment experience (naïve, or categories of prior interferon [IFN]-based therapy), and IFN eligibility (intolerant, ineligible, or eligible) and to assess the change from baseline in patient-reported outcomes (PROs) following treatment (assessed by Short-Form 36 Version 2 health survey [SF-36v2] and HCV patient-reported outcomes [HCV-PRO] questionnaires).</p>	
<p>Methodology:</p> <p>This was a Phase 3b, open-label, multicenter study evaluating the proportion of subjects with chronic HCV GT1-infection who achieved SVR₁₂ following treatment with ombitasvir/paritaprevir/ritonavir and dasabuvir (i.e., 3 direct-acting antiviral agent [DAA] regimen) ± RBV. GT1b-infected subjects without cirrhosis (i.e., fibrosis stage 3) received the 3-DAA regimen without RBV and all GT1a-infected subjects and GT1b-infected subjects with compensated cirrhosis (i.e., fibrosis stage 4) received the 3-DAA regimen with RBV.</p> <p>The study consisted of a 12 or 24 week Treatment Period during which eligible subjects received the 3-DAA regimen ± RBV, and a 24-week Post-Treatment (PT) Period. The dose of ombitasvir/paritaprevir/ritonavir was 25 mg/150 mg/100 mg once daily (QD), dasabuvir was 250 mg twice daily (BID), and RBV was 1000 mg or 1200 mg daily, based on body weight. The treatment duration was 12 weeks for all subjects except HCV GT1a-infected prior pegylated interferon (pegIFN)/RBV null responder or non-responders subjects with compensated cirrhosis, who received treatment for 24 weeks.</p> <p>In the Treatment Period, subjects were assessed for antiviral response, PROs (by SF-36v2, EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L), and HCV-PRO questionnaire, and progression of liver disease as measured by change from baseline in liver stiffness measured by transient elastography (FibroScan), where available.</p> <p>In the PT Period, all subjects administered at least 1 dose of study drug were to be followed for 24 weeks to monitor for safety, antiviral response, assessment of PROs, and progression of liver disease.</p>	
<p>Number of Subjects (Planned and Analyzed):</p> <p><u>Planned:</u> Approximately 220 subjects, with the number of subjects having a baseline fibrosis stage of F3 (without cirrhosis) and F4 (compensated cirrhosis) each between 70 and 150 subjects.</p> <p><u>Analyzed:</u> 222 subjects, including 89 subjects with baseline fibrosis stage F3 and 133 subjects with baseline fibrosis stage F4.</p>	

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria:

1. Male or female at least 18 years of age at screening.
2. HCV RNA > 1,000 IU/mL at the time of screening.
3. Fibrosis stage F3 or greater, documented by one of the following:
 - Liver biopsy within 24 months prior to first dose of study drug showing presence of advanced bridging fibrosis (Metavir F3, Ishak 4, or equivalent);
 - Any previous liver biopsy showing cirrhosis (Metavir F3/4 or F4, Ishak 5 or 6, or equivalent);
 - FibroScan within 6 months prior to first dose of study drug or during screening with result ≥ 9.6 kPa; or
 - FibroTest result ≥ 0.59 at the time of screening. Note: for the purposes of determining eligibility, a liver biopsy result took precedence over a FibroScan or FibroTest result, and a FibroScan result took precedence over a FibroTest result.
4. For subjects with cirrhosis: Absence of hepatocellular carcinoma (HCC) as indicated by a negative ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI) within 3 months prior to screening or a negative ultrasound at screening. Subjects who had an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver were eligible for the study.

Main Exclusion Criteria:

1. Positive test result for hepatitis B surface antigen (HBsAg) or anti-human immunodeficiency virus (HIV) antibody.
2. Clinically significant abnormalities or co-morbidities, other than HCV infection, that made the subject an unsuitable candidate for this study or treatment with RBV in the opinion of the investigator.
3. Any current or past clinical evidence of Child-Pugh B or C classification or clinical history of liver decompensation such as ascites (noted on physical exam), variceal bleeding, or hepatic encephalopathy.
4. History of solid organ transplant.
5. Screening laboratory analyses showing any of the following abnormal laboratory results.
 - calculated creatinine clearance (using Cockcroft-Gault method) < 30 mL/min;
 - albumin < 2.8 g/dL (lower limit of normal [LLN]);
 - hemoglobin < 10 g/dL;
 - platelets < 25,000 cells/mm³;
 - total bilirubin > 3.0 mg/dL.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:			
Investigational Product	Manufacturer	Dosage Form/Mode of Administration	Bulk Lot Number
Ombitasvir/ABT-450/ Ritonavir	AbbVie	12.5/75/50 mg tablet/oral	14-005707
Dasabuvir	AbbVie	250 mg tablet/oral	14-001469
RBV	generic manufacturer	200 mg tablet/oral	14-003370
Duration of Treatment:			
Subjects received ombitasvir/paritaprevir/ritonavir and dasabuvir ± 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. The progression of liver fibrosis (assessed by FibroScan) was assessed during treatment and PT, where available.			
Resistance:			
The following resistance information was provided for subjects who did not achieve or maintain SVR ₁₂ due to virologic failure (who had HCV RNA ≥ 1000 IU/mL):			
<ul style="list-style-type: none"> • the amino acid variants at baseline at signature amino acid positions identified by population nucleotide sequencing and comparison to the prototypic reference sequence; • the amino acid variants in available post-baseline samples identified by population nucleotide sequencing and comparison to the baseline sequence; • the amino acid variants in available post-baseline samples at signature amino acid positions identified by population nucleotide sequencing and comparison to the prototypic reference sequence. 			
Patient-Reported Outcomes:			
Patient reported outcomes were assessed using the SF-36 v2, EQ-5D-5L, and HCV-PRO questionnaires at various visits throughout the study.			
Pharmacokinetics:			
Individual plasma concentrations of ombitasvir, dasabuvir, dasabuvir M1, paritaprevir, RBV, and ritonavir were determined at each visit through the end of the Treatment Period (Week 12 or Week 24).			
Safety:			
Safety and tolerability were assessed by monitoring adverse events, physical examinations, clinical laboratory tests, electrocardiogram (ECG), and vital signs.			

Statistical Methods

Efficacy, safety, and demographic analyses were performed on the intent-to-treat (ITT) population, consisting of all subjects who received at least one dose of study drug.

Efficacy:

Primary Endpoint

The primary efficacy endpoint was the proportion of subjects achieving SVR₁₂, in adults with GT1 chronic HCV infection and Metavir equivalent fibrosis stage of F3 or F4 who received treatment with ombitasvir/paritaprevir/ritonavir and dasabuvir with or without RBV for 12 or 24 weeks. The SVR₁₂ rate and corresponding 2-sided 95% confidence interval (CI) using the Wilson score method for the binomial proportion were presented.

Secondary Endpoints

The percentage of subjects achieving SVR₁₂ by fibrosis score (F3 and F4), prior HCV treatment experience (naïve, or categories of prior IFN-based therapy), and IFN eligibility (ineligible, intolerable, eligible) and 2-sided 95% CI (using Wilson score method) for each subgroup were calculated.

Mean change from baseline in PRO scores to the PT Week 12 in SF-36v2 physical and mental component summary scores, and HCV-PRO total score were compared across baseline fibrosis stages stratified by SVR₁₂ status using analysis of covariance (ANCOVA) with baseline fibrosis stage, SVR₁₂ status, and the interaction between baseline fibrosis stages and SVR₁₂ status as factors, and appropriate baseline PRO score as a covariate.

Resistance:

For subjects receiving study drugs who experienced virologic failure (who had HCV RNA ≥ 1000 IU/mL), the amino acid polymorphisms at baseline at signature amino acid positions identified by population nucleotide sequencing compared to the prototypic reference sequence, the amino acid substitutions in available post-baseline samples identified by population nucleotide sequencing compared to the baseline sequence, and the amino acid substitutions in available post-baseline samples at signature amino acid positions identified by population nucleotide sequencing compared to the prototypic reference were to be summarized.

In addition, the persistence of treatment-emergent substitutions was evaluated in selected samples during the 24-week PT Period.

Patient-Reported Outcomes:

Exploratory analyses of change in PROs were measured using the SF-36v2, HCV PRO, and EQ-5D-5L instruments. Differences between baseline fibrosis stage groups and by SVR₁₂ status in mean change from baseline to PT Week 12 and to PT Week 24 in the PRO summary measures were analyzed using ANCOVA with baseline fibrosis stage (F3 and F4), SVR₁₂ status, and interaction between fibrosis stage and SVR₁₂ status as factors and baseline PRO score as a covariate.

A minimally important difference of -5 units was used for the change from baseline to the Final Treatment Visit in the SF-36v2 physical and mental component scores. The percentage of subjects with a change from baseline to the Final Treatment Visit > -5 was presented along with 95% CIs.

For subjects with available FibroScan results, the mean change from baseline to PT Week 12 in liver stiffness was compared between those who achieved SVR₁₂ versus those who do not using analysis of variance (ANOVA) with baseline fibrosis stage, SVR₁₂ status, and interaction between fibrosis stage and SVR₁₂ status as factors.

Statistical Methods (Continued)

Pharmacokinetics:

Plasma concentrations of paritaprevir, dasabuvir, dasabuvir M1 metabolite, ombitasvir, ritonavir, and RBV and time since last dose were listed for each subject. C_{trough} was calculated by binning of the concentrations in time interval of > 22 – 26 hours for QD drugs and > 10 to 14 hours for BID drugs based on time after last dose. Summary statistics for concentrations in each time interval were computed by analyte.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA[®]) (version 19.0). 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 in 214 of 222 (96.4%) subjects (refer to table on next page). While some differences in SVR₁₂ rates were observed across subgroups based on demographic and baseline characteristics (e.g., fibrosis status, prior HCV treatment status, IFN eligibility) in various analyses, these were generally small and not considered clinically significant.

Sustained virologic response 24 weeks postdosing (SVR₂₄) was achieved by 212 of 222 (95.5%) subjects, with 99.1% agreement between SVR₁₂ and SVR₂₄.

One (0.5%) subject experienced on treatment virologic failure (i.e., breakthrough) and 6 (2.7%) subjects relapsed PT: 3 each during the SVR₄ and SVR₁₂ assessment windows, and none thereafter. One subject did not achieve either SVR₁₂ or SVR₂₄ due to missing SVR₁₂ or SVR₂₄ data, respectively, as a result of being lost to follow-up at PT Day 35 (Study Day 120). Two other subjects achieved SVR₁₂ but did not achieve SVR₂₄ due to missing SVR₂₄ data: 1 subject moved out of the country and withdrew consent at PT Day 161 (Study Day 246) and the other subject discontinued the study at PT Day 91 (Study Day 168) due to adverse events and subsequently died on PT Day 155 (Study Day 232) due to hepatocellular carcinoma. All 3 subjects who did not achieve SVR₂₄ were assigned to 12 weeks of treatment per protocol.

Summary/Conclusions (Continued)		
Efficacy Results (Continued):		
Virologic Response (SVR₁₂, SVR₂₄) for Subjects Treated with 3-DAA, With or Without RBV (ITT Population)		
Virologic Finding	SVR₁₂	SVR₂₄
SVR, n/N (%)	214/222 (96.4)	212/222 (95.5)
95% CI ^a (%)	93.1, 98.2	91.9, 97.5
Nonresponders, n/N (%)	8/222 (3.6)	10/222 (4.5)
Reason for nonresponse, n/N (%)		
On-treatment virologic failure	1/222 (0.5)	1/222 (0.5)
Breakthrough	1/222 (0.5)	1/222 (0.5)
Fail to suppress	0/222	0/222
Relapse by PT Week 12	6/220 (2.7)	6/220 (2.7)
Relapse by PT Week 24	NA	0/212
Premature study drug discontinuation	0/222	0/222
HCV reinfection	0/221	0/221 ^b
Missing SVR ₁₂ /SVR ₂₄ data	1/222 (0.5)	3/222 (1.4)
Other	0/222	0/222
<p>BID = twice daily; CI = confidence interval; DAA = direct-acting antiviral agent; NA = not applicable; PT = post-treatment; QD = once daily; RBV = ribavirin; SVR = sustained virologic response; SVR₁₂ = sustained virologic response at 12 weeks postdosing; SVR₂₄ = sustained virologic response at 24 weeks postdosing</p> <p>a. Calculated using the Wilson score method.</p> <p>b. One subject who had HCV RNA > LLOQ at the Final Treatment Visit (due to on-treatment failure) was not included in the denominator.</p> <p>Note: 3-DAA ± RBV = ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD + dasabuvir 250 mg BID with or without RBV for 12 weeks or 24 weeks.</p>		
Resistance Results:		
<p>Resistance analyses were conducted on 7 subjects who experienced virologic failure: 1 treated with ombitasvir/paritaprevir/ritonavir and dasabuvir for 12 weeks, 5 treated with ombitasvir/paritaprevir/ritonavir and dasabuvir + RBV for 12 weeks, and 1 treated with ombitasvir/paritaprevir/ritonavir and dasabuvir + RBV for 24 weeks.</p> <p>The GT1b-infected subject who experienced virologic failure (ombitasvir/paritaprevir/ritonavir and dasabuvir 12-weeks) had Y93H in NS5A and C316N in NS5B at baseline. Treatment-emergent substitutions were not detected in NS3 or NS5A, and M414I was detected in NS5B, which persisted through the PT Week 24 time point.</p>		

Summary/Conclusions (Continued)

Resistance Results (Continued):

Among the 6 GT1a-infected virologic failures, treatment-emergent substitutions V36M, Q80L, R155K, or D168V in NS3 were detected in 5 subjects, and these persisted through PT Week 24 in 2 of 4 subjects (50%). Treatment-emergent substitutions M28T or Q30R in NS5A were detected in 5 subjects and persisted through PT Week 24 in 4 of 4 subjects. One subject had M28V and Q30R in NS5A at baseline, time of virologic failure, and PT Week 24. Treatment-emergent substitutions C316Y, M414I, G554D, A553V, or S556G in NS5B were detected in 3 subjects, and most substitutions persisted through PT Week 24 in all 3 subjects.

Overall, treatment-emergent substitutions in NS3, NS5A, or NS5B were detected in all subjects experiencing virologic failure. Substitutions in NS3 declined through PT Week 24, while those in NS5A or NS5B persisted through PT Week 24.

PRO Results:

Mean change from baseline to the PT Week 12 Visit in PRO scores (SF-36v2 Mental and Physical Component Summary scores and HCV-PRO total score) were summarized by SVR₁₂ status and fibrosis stage. Small mean increases (improvements) were seen in all 3 summary measures in subjects who achieved SVR₁₂ regardless of fibrosis stage; there was little change in the summary measures for subjects who did not achieve SVR₁₂. No statistically significant differences were observed between subjects without cirrhosis (baseline fibrosis stage 3) and subjects with compensated cirrhosis (baseline fibrosis stage 4) based on mean change from baseline in PRO scores to the PT Week 12 visit, after controlling for SVR₁₂ status and appropriate baseline PRO score. Subjects with fibrosis stage 4 showed numerically greater mean increases in the SF-36v2 Physical Component Summary, but this difference was not statistically significant.

Pharmacokinetic Results:

Non-cirrhotic and cirrhotic subjects had generally comparable exposures for all analytes, except that the geometric mean for paritaprevir in cirrhotic subjects was approximately 110% higher than that in non-cirrhotic subjects, while the individual ranges overlapped. This is consistent with the population pharmacokinetic analysis of Phase 3 data in HCV subjects, which showed that the presence of compensated cirrhosis increased paritaprevir exposures by up to 140%.

Safety Results:

Treatment-emergent adverse events were mild or moderate in severity with the exception of events reported for 9 (4.1%) subjects who experienced severe TEAEs.

The most common ($\geq 10.0\%$ of subjects) TEAEs were fatigue, headache, nausea, and pruritus. These events were generally assessed as mild in severity and having a reasonable possibility of being related to DAA treatment.

One (0.5%) subject discontinued study drug due to a TEAE; the investigator assessed the event as having no reasonable possibility of being related to DAA treatment.

A low frequency (2.7%) of serious adverse events was reported. No commonality was evident among the reported serious events. None of these events was assessed by the investigator as having a reasonable possibility of being related to DAA treatment, with the exception of 1 event of severe hepatic failure with onset on PT Day 10 and resolution after 10 days.

No fatal TEAEs were reported.

Summary/Conclusions (Continued)

Safety Results (Continued):

None of the subjects experienced a grade 3 or higher elevation of alanine aminotransferase during the study; 12 (5.4%) subjects experienced a grade 3 or higher total bilirubin elevation. These bilirubin elevations were in general asymptomatic, and none led to study drug interruption or discontinuation. Bilirubin-related events of jaundice and ocular icterus were reported with low frequency (1.4%, 3/222). There was no Hy's law case.

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

Conclusions:

- SVR₁₂ was achieved by 96.4% subjects who received the ombitasvir/paritaprevir/ritonavir and dasabuvir ± RBV regimen for 12 or 24 weeks, with a 95% CI of (93.1%, 98.2%). SVR₁₂ rate was high (> 96%), regardless of fibrosis stage (F3 or F4) and prior HCV treatment (naïve or IFN-based treatment experienced).
- Non-cirrhotic and cirrhotic subjects had generally comparable exposures for all analytes, except paritaprevir, for which the geometric mean in cirrhotic subjects was approximately 110% higher than that in non-cirrhotic subjects.
- Ombitasvir/paritaprevir/ritonavir and dasabuvir ± RBV was well-tolerated, demonstrating a favorable safety profile among adults in Brazil with chronic HCV GT1 infection.