2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: ABT-450, ritonavir, ABT-267, ribavirin	**Volume:** **Page:**	
Name of Active Ingredient: **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,14,15,16,16 atetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate **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 **ABT-267:** Dimethyl ([(2S,5S)-1-(4-tertbutylphenyl) pyrrolidine-2,5-[diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate **Ribavirin:** 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide		

Title of Study:

An Open-Label Study to Evaluate the Safety and Efficacy of the Coadministration of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) with Ribavirin (RBV) in Adults with Chronic Hepatitis C Virus Genotype 4 Infection in Egypt

Coordinating Investigator:

Professor Gamal Eldin Esmat

Study Sites:

Five investigative sites in Egypt

Publications: 3 abstracts and 1 article	
Studied Period (Years): First Subject First Visit: 04 November 2014 Last Subject Last Visit: 01 August 2016	**Phase of Development:** 3

Objectives:

The primary objective of this study was to assess the efficacy (the percentage of subjects with hepatitis C virus [HCV] ribonucleic acid [RNA] < lower limit of quantitation [LLOQ] 12 weeks after the last actual dose of study drug [SVR_{12}]) and safety of ABT-450/ritonavir (r)/ABT-267 coadministered with RBV among treatment-naïve and prior pegylated-interferon (pegIFN)/RBV treatment-experienced HCV genotype (GT)4-infected subjects without cirrhosis or with compensated cirrhosis. Secondary objectives of this study were to assess the percentage of subjects with on-treatment virologic failure in each treatment arm, and to assess the percentage of subjects experiencing post-treatment relapse within 12 weeks following end of treatment ($Relapse_{12}$) in each treatment arm.

Methodology:

This was a Phase 3, open-label, multicenter study evaluating the efficacy and safety of ABT-450/r/ABT-267 coadministered with weight-based RBV in HCV GT4-infected adults who were treatment-naïve or treatment-experienced to pegIFN/RBV treatment. The study consisted of 2 periods (not including a screening period of up to 35 days), a Treatment Period, and Post-Treatment Period. In addition, this study was divided into 2 separate substudies that were open to enrollment in parallel. Substudy 1 consisted of a single arm (Arm A) of HCV GT4-infected treatment-naïve and treatment-experienced subjects without cirrhosis who were stratified by prior pegIFN/RBV treatment experience and received study drug for 12 weeks of treatment. Substudy 2 consisted of HCV GT4-infected treatment-naïve and treatment-experienced subjects with compensated cirrhosis who were randomly assigned in a 1:1 allocation ratio to receive study drug for either 12 weeks of treatment (Arm B) or 24 weeks of treatment (Arm C). Randomization was stratified by prior pegIFN/RBV treatment experience, and was further stratified in treatment-experienced subjects by type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) as follows:

- Null responder: received at least 10 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a 2 $\log_{10}$ IU/mL reduction in HCV RNA at Week 12 (subjects were considered to meet this definition if the lack of treatment response was documented between Weeks 10 – 16 of treatment); or received at least 4 weeks of pegIFN/RBV for the treatment of HCV and achieved a < 1 $\log_{10}$ IU/mL reduction in HCV RNA at Week 4 (subjects were considered to meet this definition if the lack of treatment response was documented after ≥ 25 days of treatment).

- Partial responder: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved ≥ 2 $\log_{10}$ reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment.

- Relapser: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at or after the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up.

Safety and efficacy evaluations occurred throughout the study. During the Post-Treatment Period, subjects who completed or prematurely discontinued study drug were followed for 48 weeks to monitor safety and HCV RNA, and to assess patient reported outcomes (PROs).

Number of Subjects (Planned and Analyzed):

Planned: Approximately 160 subjects: 100 without cirrhosis in Arm A (50 treatment-naïve and 50 treatment-experienced) and 60 with compensated cirrhosis in Arms B and C (at least 20 treatment-experienced with the remainder treatment-naïve).

Analyzed: 160 subjects enrolled and received at least 1 dose of study drug (100 enrolled in Arm A, 31 randomized to Arm B, and 29 randomized to Arm C).

Diagnosis and Main Criteria for Inclusion:

All subjects were at least 18 years of age and had a chronic HCV GT4 infection (positive for anti-HCV antibody or HCV RNA > 1,000 IU/mL at least 6 months before screening, and positive for HCV RNA and anti-HCV antibody 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]).

The study population for Arm A consisted of HCV GT4-infected noncirrhotic adult subjects with documented liver biopsy within 24 months prior to screening or during screening demonstrating the absence of cirrhosis, or, in the absence of a biopsy, a screening FibroTest score of ≤ 0.72 and aspartate aminotransferase-to-platelet ratio index (APRI) ≤ 2; or a screening transient elastography (e.g., FibroScan®) result of < 12.5 kPa.

The study population for Arms B and C consisted of HCV GT4-infected adult subjects with compensated cirrhosis (defined as Child-Pugh score ≤ 6 at screening). Documentation of cirrhosis included previous histologic diagnosis on liver biopsy, e.g., Metavir Fibrosis Score of > 3 (including 3 – 4 or 3/4), Ishak score of > 4 on a liver biopsy conducted during screening; or a transient elastography (e.g., FibroScan) score ≥ 14.6 kPa within 6 months of screening or during the screening period; or a screening FibroTest > 0.72 and APRI > 2. Additionally, the 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 were required (subjects with an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver were eligible for the study).

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

Investigational Product	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
ABT-450/ Ritonavir/ ABT-267	Oral	Tablet	75 mg/ 50 mg/ 12.5 mg	13-001960
Ribavirin	Oral	Tablet	200 mg	13-002244 13-002247

Duration of Treatment:

In Arm A, treatment-naïve and treatment-experienced subjects without cirrhosis received ABT-450/r/ABT-267 with RBV for 12 weeks. In Arm B, treatment-naïve and treatment-experienced subjects with compensated cirrhosis received ABT-450/r/ABT-267 with RBV for 12 weeks. In Arm C, treatment-naïve and treatment-experienced subjects with compensated cirrhosis received ABT-450/r/ABT-267 with RBV for 24 weeks.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:
Not applicable.

Criteria for Evaluation

Efficacy:

Virologic response was assessed by HCV RNA in $\log_{10}$ IU/mL at various time points from Study Day 1 through 48 weeks after completion of treatment.

Patient-Reported Outcomes:

General health related quality of life (HRQoL) was assessed by using a self-administered, Short Form 36, version 2 (SF-36v2) non-disease-specific health survey. Impact on subjects' health state utility was assessed by the self-administered EuroQol-5 Dimensions-5 Levels health state instrument (EQ-5D-5L). Impact on disease-specific function and wellbeing was assessed by a self-administered Hepatitis C Virus Patient Reported Outcomes Instrument (HCV-PRO).

Safety:

Safety and tolerability were assessed by monitoring adverse events (AEs), vital signs, physical examination, and laboratory test assessments.

Statistical Methods

All subjects who received at least 1 dose of study drug were included in summaries of demographics, baseline characteristics, efficacy, and safety. Baseline was the last nonmissing observation before the first dose of study drug. All statistical tests were two-sided with an α level of 0.05. Confidence intervals (CIs) for efficacy endpoints were constructed using the Wilson score method.

Efficacy:

The primary efficacy endpoint was the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in each treatment arm.

The secondary efficacy endpoints were:

- the percentage of subjects in each treatment arm experiencing on-treatment virologic failure, and
- the percentage of subjects in each treatment arm experiencing post-treatment relapse within 12 weeks following end of treatment ($Relapse_{12}$).

For each treatment arm, the number and percentage of subjects meeting each primary and secondary endpoint were summarized along with the estimated 95% CIs. Additionally, the SVR_{12} rate in Arms B and C were compared using stratum-adjusted Mantel-Haenszel proportions and continuity-corrected variances, adjusting for previous PegIFN/RBV treatment category (naïve, null responder, partial responder, or relapser). Subgroup analyses of the primary efficacy variable of SVR_{12} were performed. The number and percentage of subjects achieving SVR_{12} and the corresponding 2-sided 95% CI within each subgroup was presented for each treatment arm.

Statistical Methods (Continued)

Patient-Reported Outcomes:

Summary statistics (n, mean, standard deviation [SD], median, minimum and maximum) at each applicable visit and for change from baseline to each applicable visit by treatment arm were provided for the following PRO endpoints: SF36v2 Mental Component Summary score, SF36v2 Physical Component Summary score, SF36v2 domain score, HCV-PRO total score, and EQ-5D-5L health index score and visual analog scale (VAS) score. Subject's responses to the EQ-5D-5L were combined into a unique health state using a 5-digit code with 1 digit from each of the 5 dimensions. The EQ-5D-5L states were converted into a single preference-weighted health utility index score by applying the weights for the United States of America. The VAS score was measured separately.

Safety:

All subjects who received at least 1 dose of study drug were included in the safety analyses. Data were summarized by descriptive statistics for each treatment arm.

The number and percentage of subjects reporting treatment-emergent AEs were tabulated by Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and preferred term for each treatment group. Tabulations were also provided in which the number of subjects reporting an AE (MedDRA term) was additionally presented by severity and relationship to direct-acting antiviral agents (DAAs) and to RBV. 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 within each treatment group with PCS values were calculated. Similar summaries were prepared for hemoglobin and liver function tests by Common Terminology Criteria for Adverse Events Grade.

Summary/Conclusions

Efficacy Results:

The primary efficacy endpoint in this study was the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drugs). In subjects treated for 12 weeks in noncirrhotic Arm A, the SVR_{12} rate was 94.0% with a corresponding 95% CI of 87.5% – 97.2%. The SVR_{12} rate was 96.8% with a corresponding 95% CI of 83.8% – 99.4% for subjects treated for 12 weeks in cirrhotic Arm B and 93.1% with a corresponding 95% CI of 78.0% – 98.1% for subjects treated for 24 weeks in cirrhotic Arm C. Excluding nonvirologic failures, SVR_{12} rates were 95.9%, 96.8%, and 96.4%, respectively. The data indicate that the SVR rate did not improve when treatment was extended from 12 weeks to 24 weeks.

Sensitivity analyses of SVR_{12} that evaluated alternative methods to impute missing virologic results were consistent with the primary analysis. Additionally, the difference in SVR_{12} rate in Arms B and C after adjustment for previous pegIFN/RBV treatment category (naïve, null responder, partial responder, or relapser) was not statistically significant based on stratum adjusted Mantel-Haenszel proportions and continuity-corrected variances.

No subjects failed to suppress during treatment. One subject in each treatment arm experienced on-treatment virologic breakthrough by Week 10 and therefore would not have benefited from a longer duration of treatment. Three subjects in Arm A, who completed treatment and had HCV RNA < LLOQ at the end of treatment, relapsed within 4 weeks after the last actual dose of study drug; no subject in Arm B or Arm C experienced relapse.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Sustained virologic response at 24 weeks after the last actual dose of study drug (SVR_{24}) was the same as at Post-Treatment Week 12; the concordance between SVR_{12} and SVR_{24} was 100%.

Given only 9 subjects across Arms A, B, and C did not achieve SVR_{12}, the SVR_{12} rates within subgroups were generally high, consistent with those of the overall intent-to-treat population, and without clinically meaningful differences between the subgroups.

Patient-Reported Outcomes Results:

None of the PROs showed improvement from baseline to the Final Treatment Visit; however, all showed numerical improvements at the Final Post-Treatment Visit with the exception of the EQ-5D-5L health index score, which was basically unchanged from baseline. Score changes from baseline were not statistically significantly different between Arms B and C for any PRO.

Safety Results:

Both 12-week and 24-week 2-DAA regimens with RBV were generally well tolerated, with no subject discontinuing DAAs due to a treatment-emergent AE. The majority of subjects in each treatment arm experienced at least 1 treatment-emergent AE. Adverse events occurring in $\geq 10\%$ of subjects overall were headache, fatigue, pruritus, dyspepsia, abdominal pain upper, cough, and insomnia. Statistically significantly greater percentages of subjects in Arm C experienced decreased appetite (13.8%) and chromaturia (17.2%) compared with subjects in Arm B (0% for both events). However, all decreased appetite and chromaturia events started within the first 12 weeks of treatment; therefore, the higher rate observed in Arm C was incidental and not related to the longer duration of treatment.

Overall, the majority of treatment-emergent AEs were mild or moderate in severity.

Four subjects (2 in Arm A and 2 in Arm C) experienced a total of 5 treatment-emergent serious AEs (SAEs). All were singular events (apnoea, deep vein thrombosis, and oesophageal varices haemorrhage in 1 subject each, and bile duct stone and cholecystitis acute both in 1 subject). Deep vein thrombosis was the only SAE considered by the investigator to have a reasonable possibility of relationship to DAA and RBV.

Twenty-two subjects (11.0% Arm A, 12.9% Arm B, 24.1% Arm C) experienced a treatment-emergent AE leading to RBV dose modification. The most common treatment emergent AE leading to RBV dose modification was anaemia. All subjects requiring RBV dose modification achieved SVR_{12}.

Overall, the percentage of subjects in any treatment arm who experienced a PCS or Grade > 1 hematology or chemistry values was low for all analytes except for total bilirubin. The majority (56.3%) of subjects had a postbaseline minimum hemoglobin value that was Grade 1; 8.1% of subjects had a postbaseline minimum hemoglobin value that was Grade 2. No subjects experienced a Grade 3 or 4 hemoglobin value.

No subject experienced a Grade 2 or higher alanine aminotransferase or aspartate aminotransferase value during the Treatment Period. Eight subjects (2 [2.0%] in Arm A, 2 [6.5%] in Arm B, and 4 [13.8%] in Arm C) experienced a postbaseline Grade 3 bilirubin level. Seven of these subjects had bilirubin values resolve or return to Grades 1 or 2 while continuing DAAs. Additionally, higher rates of Grade 3 bilirubin elevations were observed among subjects in cirrhotic Arms B and C (10.0%) compared with subjects in noncirrhotic Arm A (2.0%).

Summary/Conclusions (Continued)

Conclusions:

In HCV GT4-infected Egyptian subjects treated with ABT-450/r/ABT-267 coadministered with RBV, high SVR_{12} rates of 94.0%, 96.8%, and 93.1% were observed in Arm A (noncirrhotic, 12 weeks of treatment), Arm B (cirrhotic, 12 weeks of treatment), and Arm C (cirrhotic, 24 weeks of treatment), respectively.

Both 12-week and 24-week 2-DAA regimens with RBV were generally well tolerated in subjects with and without compensated cirrhosis, with no subject discontinuing DAAs due to a treatment-emergent AE. The majority of events in all treatment arms were mild or moderate in severity.

High SVR_{12} rates were achieved in HCV GT4-infected treatment-naïve and treatment experienced (e.g., pegIFN/RBV) Egyptian subjects without cirrhosis and with compensated cirrhosis who received ABT-450/r/ABT-267 150/100/25 mg QD + RBV BID for 12 weeks, and extending treatment to 24 weeks for subjects with compensated cirrhosis did not provide an additional efficacy benefit.