

Synopsis

<p>AbbVie Inc.</p>	<p>Individual Study Table Referring to Part of Dossier:</p>	<p>(For National Authority Use Only)</p>
<p>Name of Study Drug: Ombitasvir/ABT-450/ritonavir, ribavirin</p>	<p>Volume:</p> <p>Page:</p>	
<p>Name of Active Ingredient:</p> <p><u>Ombitasvir:</u> Dimethyl ((2S,5S)-1-(4-tert-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><u>ABT-450:</u> (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-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate</p> <p><u>Ritonavir:</u> [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><u>Ribavirin:</u> 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide</p>		
<p>Title of Study: A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir Co-administered with Ribavirin (RBV) in Adults with Genotype 4 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (AGATE-I)</p>		

Coordinating Investigator: Professor ██████████ MD, PhD	
Study Sites: 29 investigative sites in Austria, Belgium, Canada, France, Germany, Greece, Italy, Spain, and the United States enrolled subjects	
Publications: 2 abstracts and 1 paper	
Studied Period (Years): First Subject First Visit: 28 October 2014 Last Subject Last Visit: 07 April 2017	Phase of Development: 3
Objectives: <p>The primary objectives of this study in HCV genotype 4 (GT4)-infected subjects with compensated cirrhosis receiving treatment with coformulated ombitasvir/ABT-450/ritonavir (r) coadministered with RBV for 12, 16, or 24 weeks were to assess the safety and to compare the percentage of subjects, who were either treatment-naïve or who had previously received only interferon (IFN)/RBV treatment for HCV, achieving a 12-week sustained virologic response (SVR), SVR 12 weeks postdosing (SVR₁₂, HCV ribonucleic acid [RNA] < lower limit of quantification [LLOQ] 12 weeks following treatment) to a clinically relevant threshold (based on historic SVR rates for HCV GT4-infected subjects treated with pegylated interferon [pegIFN]/RBV).</p> <p>The secondary objectives of this study were to assess the following in HCV GT4-infected subjects with compensated cirrhosis who were either treatment-naïve or who had previously received only IFN/RBV treatment for HCV: comparison of the SVR₁₂ following 12 weeks of treatment (Arm A) to the SVR₁₂ following 16 weeks of treatment (Arm B); comparison of the SVR₁₂ following 16 weeks of treatment (Arm B) to the SVR₁₂ following 24 weeks of treatment (Arm C); assessment of the percentage of subjects with on-treatment virologic failure during 12, 16, or 24 weeks of treatment (each of Arms A, B, and C); and assessment of the percentage of subjects experiencing post-treatment relapse within 12 weeks following the end of either 12, 16, or 24 weeks of treatment (each of Arms A, B, and C).</p>	
Methodology: <p>This is a Phase 3, randomized, open-label, multicenter study evaluating the safety and efficacy of ombitasvir/ABT-450/r coadministered with RBV for 12, 16, or 24 weeks in HCV GT4-infected adults with compensated cirrhosis. This study was divided into 2 parts. Part I included subjects who received either 12 weeks (Arm A) or 16 weeks (Arm B) of treatment and Part II included subjects who received 24 weeks of treatment (Arms C and D). Arms A and B comprised subjects who were HCV GT4-infected and either treatment-naïve or treatment-experienced with IFN/RBV only. Arm C comprised subjects who were HCV GT4-infected and either treatment-naïve or treatment-experienced with IFN/RBV only. Arm D comprised subjects who were HCV GT4-infected and sofosbuvir (SOF)/pegylated IFN (pegIFN)/RBV or SOF/RBV treatment failures. The study consisted of 2 periods (not including a screening period of up to 35 days), a Treatment Period, and Post-Treatment Period.</p> <p>Enrollment into Part II of the study (Arms C and D) was opened after randomization was completed for Part I. There was no randomization in Part II.</p>	

Methodology (Continued):

Subjects in Arms A, B, and C were stratified by treatment history – either treatment-experienced with previous IFN/RBV or treatment-naïve. The treatment-experienced subjects were stratified by type of nonresponse to previous IFN/RBV treatment (null responders, partial responders, or relapsers). An approximately equal number of treatment-naïve subjects and IFN/RBV treatment-experienced subjects were allowed to enroll in Arms A, B, and C. Prior HCV therapy must have been completed no less than 2 months prior to the Screening Visit.

The categories of type of nonresponse to previous IFN/RBV treatment-experienced subjects in Arms A, B, and C were defined as follows:

Null responder:

- received at least 10 weeks of IFN/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 and 16 of treatment); or
- received at least 4 weeks of IFN/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 IFN/RBV for the treatment of HCV and achieved $\geq 2 \log_{10}$ 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 IFN/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.

The treatment-experienced subjects in Arm D were defined as follows:

- prior SOF breakthrough/nonresponder: HCV RNA detectable at the end of treatment with SOF/pegIFN/RBV or SOF/RBV;
- prior SOF relapser: achieved HCV RNA undetectable at end of a prior treatment course SOF/pegIFN/RBV or SOF/RBV, but HCV RNA was detectable within 52 weeks following completion of therapy.

During the Post-Treatment Period, subjects who completed or prematurely discontinued study drug were followed for 48 weeks to monitor safety, persistence of virologic response, HCV RNA, the emergence and persistence of viral variants in those who experienced virologic failure, and assessment of patient reported outcomes (PROs).

Safety and efficacy evaluations occurred throughout the study. Virologic stopping criteria were evaluated for individual subjects. Efficacy evaluations were conducted to evaluate if the duration of treatment needed to be extended based on rates of relapse; no treatment adjustment criteria were met. Interim summaries of safety data were provided to an independent Data Monitoring Committee for further review throughout the study.

A primary analysis clinical study report (CSR) presenting efficacy and safety data from subjects participating in Part I of the study through the Post-Treatment Week 12 Visit was completed. Subjects in Part II had not yet completed the Treatment Period at the time of the database lock for the Part I primary analysis CSR. All final, cumulative efficacy and safety data through Post-Treatment Week 48 for subjects in both Parts I and II are included in this final CSR.

Number of Subjects (Planned and Analyzed):

One hundred twenty subjects were planned to be randomized in a 1:1 ratio to a 12- or 16 week treatment duration arm with 60 subjects per arm in Part I. After Part I was completely enrolled, Part II was to enroll 60 subjects to Arm C and a maximum of 10 subjects to Arm D.

A total of 184 subjects were enrolled: 120 randomized in Part I (59 in Arm A and 61 in Arm B) and 64 enrolled in Part II (61 in Arm C and 3 in Arm D).

Diagnosis and Main Criteria for Inclusion:

The study population for Arms A, B, and C consisted of HCV GT4-infected adult subjects with compensated cirrhosis (defined as Child-Pugh score ≤ 6 at screening) who were either treatment-naïve or had only received IFN/RBV for treatment of HCV. The study population for Arm D included HCV GT4-infected adult subjects with compensated cirrhosis who experienced treatment virologic failure with either SOF/pegIFN/RBV or SOF/RBV. 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]) and documentation of cirrhosis (e.g., a Metavir score > 3 or an Ishak score > 4 , FibroScan[®] result ≥ 14.6 kPa, or screening FibroTest > 0.72 and an aspartate aminotransferase-to-platelet ratio index > 2).

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

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
Ombitasvir/ ABT-450/ Ritonavir	AbbVie	Oral	Tablet	12.5 mg/ 75 mg/ 50 mg	14-002317
Ribavirin	Roche or Kadmon Pharmaceuticals, LLC	Oral	Tablet	200 mg	14-001215 14-002828

Duration of Treatment:

Subjects received ombitasvir/ABT-450/r with RBV for 12, 16, or 24 weeks.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Not applicable.

Criteria for Evaluation

Efficacy:

Plasma HCV RNA in IU/mL was assessed at all Treatment Period visits and at all Post-Treatment Visits.

Resistance:

For subjects who did not achieve SVR₁₂, the variants at each signature resistance-associated amino acid position by population nucleotide sequencing at baseline compared with the appropriate prototypic reference sequence, and the variants at each amino acid position by population and/or next-generation sequencing at available postbaseline time points compared with baseline and the appropriate prototypic reference sequences were tabulated and summarized.

Patient-Reported Outcomes:

The change in disease-specific function and wellbeing were assessed using the HCV Patient-Reported Outcomes (HCV-PRO) instrument. 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) nondisease specific HRQoL instrument.

Pharmacokinetic:

Plasma concentrations for ombitasvir, ABT-450, ritonavir, and RBV were tabulated and summarized. Ombitasvir and ABT-450 metabolites were not assayed.

Safety:

Safety and tolerability were assessed by monitoring adverse events (AEs), physical examinations, clinical laboratory tests, 12-lead electrocardiograms, and vital signs.

Statistical Methods

Efficacy:

The primary efficacy endpoints were the percentage of subjects with SVR₁₂ within Arms A, B, and C. The overall 2-sided significance level of 0.05 was split between Part I (Arms A and B) and Part II (Arm C) using a Bonferroni-corrected alpha level of 0.025 for each part. Statistical testing within Part II is independent of the testing within Part I. The percentage of subjects achieving SVR₁₂ within Arms A, B, and C was calculated and a 2-sided 97.5% confidence interval (CI) of the percentage was computed using the Wilson score method.

In order to control the Bonferroni-corrected Type 1 error rate of 0.025, a fixed sequence testing procedure for Part I was used to proceed through the primary endpoints in the order below:

- A1. SVR₁₂: Superiority of Arm B to a clinically relevant threshold; the lower confidence bound (LCB) of the 97.5% CI for the percentage of subjects with SVR₁₂ in Arm B must have exceeded 67% to achieve superiority;
- A2. SVR₁₂: Superiority of Arm A to a clinically relevant threshold; the LCB of the 97.5% CI for the percentage of subjects with SVR₁₂ in Arm A must have exceeded 67% to achieve superiority.

The primary endpoint within Arm C was tested with a Bonferroni-corrected Type 1 error rate of 0.025.

- B1. SVR₁₂: Superiority of Arm C to a clinically relevant threshold; the LCB of the 97.5% CI for the percentage of subjects with SVR₁₂ in Arm C must have exceeded 67% to achieve superiority.

For each arm, the LCB of the 97.5% CI of the SVR₁₂ rate must have been greater than 67% (a clinically relevant threshold based on historical SVR rates for HCV GT4-infected subjects treated with pegIFN/RBV) in order for the regimen to be considered superior.

The secondary efficacy endpoints were:

- the percentage of subjects with SVR₁₂ in Arm B compared to Arm A;
- the percentage of subjects with SVR₁₂ in Arm C compared to Arm B;
- the percentage of subjects in Arms A, B, and C with on-treatment virologic failure during the Treatment Period (defined as breakthrough [confirmed HCV RNA \geq LLOQ after HCV RNA $<$ LLOQ during treatment] or failure to suppress during treatment [confirmed HCV RNA \geq LLOQ at the end of treatment]);
- the percentage of subjects in Arms A, B, and C with post-treatment relapse (defined as confirmed HCV RNA \geq LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects completing treatment and with HCV RNA $<$ LLOQ at the end of treatment).

Statistical Methods (Continued)

Efficacy (Continued):

If success was demonstrated for all of the primary efficacy endpoints within Part I (i.e., Arms A and B), the multiple testing procedure continued to the first secondary efficacy endpoint to compare the percentage of subjects with SVR₁₂ following 12 or 16 weeks of treatment. If success was demonstrated for the primary efficacy endpoint within Part II (Arm C), the multiple testing procedure continued to the second secondary efficacy endpoint to compare the percentage of subjects with SVR₁₂ following 16 or 24 weeks of treatment. To test the hypothesis that the percentages of subjects who achieved SVR₁₂ is different between arms, the percentages were compared using a logistic regression model with treatment arm, baseline log₁₀ HCV RNA level, and IFN/RBV treatment history (treatment-naïve or treatment-experienced) as predictors.

In addition, treatment differences (with 95% CIs) for the specified comparisons were estimated using stratum-adjusted Mantel-Haenszel proportion and continuity-corrected variance, adjusting for IFN/RBV treatment history (treatment-naïve or treatment experienced). The stratum-adjusted Mantel-Haenszel proportions were used for the primary statistical inference if the logistic regression analysis could not be completed due to complete or quasi-separation.

The percentages (with 2-sided 95% CIs using Wilson score method) of the subjects with virologic failure during treatment and post-treatment relapse were calculated and summarized. These endpoints were not part of the multiple testing procedure because no hypothesis was tested.

Resistance:

The following analyses were performed on the samples from subjects who did not achieve SVR₁₂ or SVR₂₄ and had postbaseline sequence data available: the HCV amino acid sequence, as determined by population sequencing, on the sample closest in time after failure/discontinuation or follow-up time points was compared with the baseline and appropriate prototypic reference amino acid sequences.

Patient-Reported Outcomes:

Summary statistics (n, mean, standard deviation, median, minimum and maximum) at each visit and for change from baseline to each visit by treatment arm were provided for the HCV-PRO total score, the EQ-5D-5L health index and Visual Analogue Scale (VAS) scores, and the SF-36v2 Mental Component Summary and Physical Component Summary scores. For each of these scores, mean change from Baseline to Final Treatment Visit and from Baseline to Post-Treatment Week 12 was compared between Arms A and B and between Arms B and C in the intent-to-treat (ITT) population using an analysis of covariance model with treatment arm as a factor and baseline score as a covariate.

Safety:

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; comparisons were performed between Arms A and B using Fisher's exact test. Tabulations were also provided in which the number of subjects reporting an AE (MedDRA term) in each arm 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 during the Treatment Period was summarized descriptively by treatment group. Laboratory and vital sign values that were potentially clinically significant (PCS), according to predefined criteria, were identified and the percentages of subjects with PCS values during the Treatment Period were compared between Arms A and B using Fisher's exact tests.

Summary/Conclusions

Efficacy Results:

In Arm B, the SVR₁₂ rate was 100% (61/61) with a corresponding 97.5% CI of 92.4% – 100%. As the LCB was above 67% (superiority threshold), testing continued to the second primary efficacy comparison. In Arm A, the SVR₁₂ rate was 96.6% (57/59) with a corresponding 97.5% CI of 86.7% – 99.2%. The LCB was again above 67% (superiority threshold). In Arm C, the SVR₁₂ rate was 93.4% (57/61) with a corresponding 97.5% CI of 82.6% – 97.7%. Thus, the LCB was above 67% (superiority threshold). Therefore, treatment with ombitasvir/ABT-450/r coadministered with RBV for 12, 16, and 24 weeks demonstrated superiority to the predefined clinically relevant threshold of 67% based on historical SVR rates for HCV GT4-infected subjects treated with pegIFN/RBV.

Sensitivity analyses that evaluated alternative methods to impute missing virologic results were consistent with the primary analysis.

One (1.7%) subject in Arm A experienced on-treatment virologic breakthrough and therefore would not have benefited from a longer duration of treatment. No other subject in Arm A, B, or C experienced virologic failure through the SVR₁₂ time window.

The differences in SVR₁₂ rates between Arms A and B and between Arms B and C were not statistically significant using stratum-adjusted Mantel-Haenszel proportion and continuity-corrected variance, adjusting for IFN/RBV treatment history (treatment-naïve or treatment experienced).

SVR₁₂ was achieved by 100% (3/3) of subjects in Arm D.

One subject in Arm A, who achieved SVR₁₂, subsequently relapsed at Week 24. In Arm D, sustained virologic response 24 weeks postdosing (SVR₂₄) was observed in 2 of the 3 subjects (66.7%); 1 subject who achieved SVR₁₂ was missing data in the SVR₂₄ window. No subject who achieved SVR₂₄ subsequently relapsed.

Given only 6 subjects across Arms A, B, and C did not achieve SVR₁₂, the SVR₁₂ rates within subgroups were generally high, consistent with those of the overall ITT population, and without clinically meaningful differences between the subgroups.

Resistance Results:

Resistance analyses were conducted on samples from the 2 subjects in Arm A (1 each with GT4a or GT4d infection) who experienced virologic failure. Neither subject had baseline polymorphisms in NS3, while P58L or T58P in nonstructural viral protein 5A (NS5A) were detected at baseline in the GT4a- or GT4d-infected subject, respectively. The GT4a-infected subject had treatment-emergent substitution A156K in NS3, and L28M/I, M31I, or Y93H in NS5A at the time of failure or at follow-up time points. The GT4d-infected subject had treatment emergent substitutions D168V in NS3, and K24Q and Y93H in NS5A at the time of failure.

Pharmacokinetic Results:

Exposures of ombitasvir, paritaprevir, ritonavir, and ribavirin in HCV GT4-infected adults with compensated cirrhosis are comparable among treatment arms with overlapping ranges.

Summary/Conclusions (Continued)

Patient-Reported Outcomes Results:

Not all PROs showed improvements from baseline to Final Treatment Period Visit, as the SF 36v2 Mental Component Summary and the EQ-5D-5L health index score decreased in each of the 3 treatment arms. In addition, the SF-36v2 Physical Component Summary and HCV-PRO total scores decreased in Arm C from baseline to the Final Treatment Period Visit. However, improvement in the EQ-5D-5L health index and VAS scores and in the HCV PRO total score from baseline to the Post-Treatment Week 12 Visit was observed in Arms A, B, and C.

Furthermore, score changes from baseline were not statistically significantly different between Arms A and B or between Arms B and C for most PROs. Only 2 statistically significant differences were observed among treatment arms. One was the mean change from baseline to the Final Treatment Period Visit in the SF-36 Mental Component Summary score when comparing Arms A and B. In this case, subjects in Arm B (16 weeks) had a greater score decline than subjects in Arm A (12 weeks), possibly due to being monitored for an additional 4 weeks. The other statistically significant difference was observed for the mean change from baseline to the Final Treatment Period Visit in the EQ-5D-5L VAS score when comparing Arm B to Arm C. In this case, subjects in Arm C (24 weeks) had a greater score than subjects in Arm B (16 weeks).

Safety Results:

Ombitasvir/ABT-450/r coadministered with RBV for 12, 16, or 24 weeks to HCV GT4 infected, treatment-naïve and treatment-experienced adults (previous pegIFN/RBV or virologic failure with either SOF/pegIFN/RBV or SOF/RBV) with compensated cirrhosis was generally well tolerated. The majority of subjects (80.0% 12-week treatment [Arm A], 93.3% 16-week treatment [Arm B], 89.1% 24-week treatment [Arms C + D]) experienced at least 1 AE during the Treatment Period, most of which were mild or moderate in severity. Two subjects in the 24-week treatment group prematurely discontinued study drug due to an AE (a serious adverse event [SAE] of hepatotoxicity in 1 subject and mild transaminase increased in the other subject).

Overall, there were no clinically meaningful differences in the safety profile in Arms A, B, and C + D. Adverse events reported for $\geq 10.0\%$ of all subjects were asthenia, fatigue, headache, pruritus, anemia, and nausea. Pruritus was the only event with an incidence that was statistically significantly different between the 12- and 16-week treatment groups (8.3% Arm A and 23.3% Arm B, respectively); this event was assessed as mild or moderate in severity. An evaluation of incidence by time period demonstrated that the onset of most events in each treatment group, including pruritus, began within the first 12 weeks of treatment. These results indicate that the higher rates of AEs observed for some AEs among subjects treated for 16 or 24 weeks was not due to the additional 4 to 12 weeks of therapy.

The overall incidence of SAEs (6.0%) was low, with 4 subjects each in the 12-week (Arm A) and 16-week (Arm B) treatment groups and 3 subjects in the 24-week (Arms C + D) treatment group experiencing SAEs. All SAEs were deemed not associated with the direct-acting antiviral agent (DAAs), with the exception of 1 SAE of hepatotoxicity in 1 subject in the 24-week treatment group (Arm C) that led to premature discontinuation of study drug. Serious AEs experienced by more than 1 subject overall were anemia (2 subjects in the 12-week treatment group), acute coronary syndrome (2 subjects in the 16-week treatment group), and intervertebral disc protrusion (2 subjects in the 16-week treatment group). Each of the subjects who experienced acute coronary syndrome was diabetic, had a history of cardiac disease, and required RBV dose reduction due to hemoglobin decline.

Summary/Conclusions (Continued)

Safety Results (Continued):

No subject died during the treatment period. One death was reported in Arm B approximately 33 weeks after completion of 16 weeks of study drug treatment. The subject died from "respiratory insufficiency and hypertension pulmonary" that was considered not associated with study drug treatment.

Analyses of rash-related events, liver function test values, and hepatic-related events during this study showed no new or different patterns compared with other clinical studies of AbbVie 2 DAA and 3-DAA regimens with RBV in subjects without cirrhosis or in subjects with compensated cirrhosis. Alanine aminotransferase values generally normalized during treatment, reflecting eliminating of the HCV and improved health of the liver.

Mean elevations in total bilirubin were observed in this study. Although these elevations were predominantly indirect bilirubin, some subjects had parallel increases in direct bilirubin, possibly due to decreased elimination of conjugated bilirubin associated with underlying cirrhosis. The bilirubin levels in general peaked at Week 1 and declined towards baseline by the end of treatment. Symptomatic hyperbilirubinemia was infrequent. One subject in the 12-week treatment group experienced hepatic decompensation (AEs of mild ascites and severe and serious esophageal varices hemorrhage that the investigator considered not associated with DAA treatment or RBV). One subject in the 24-week (Arm C) treatment group experienced an SAE of hepatotoxicity that led to premature discontinuation of all study drugs.

No clinically meaningful urinalysis, vital sign, or electrocardiogram results were observed.

Conclusions:

Superiority of 12, 16, and 24 weeks of ombitasvir/ABT-450/r coadministered with RBV to the predefined threshold based on the historical SVR rates for HCV GT4-infected subjects treated with pegIFN/RBV was demonstrated. SVR₁₂ was 96.6% (97.5% CI: 86.7% – 99.2%) after 12 weeks, 100% (97.5% CI: 92.4% – 100%) after 16 weeks, and 93.4% (97.5% CI: 82.6% – 97.7%) after 24 weeks of treatment. One (1.7%) subject in Arm A experienced on-treatment virologic breakthrough and, therefore, would not have benefited from a longer duration of treatment. No other subject in Arm A, B, or C experienced virologic failure through the SVR₁₂ time window. Sensitivity analyses that evaluated alternative methods to impute missing virologic results were consistent with the primary analysis. The efficacy results of this study support a 12-week duration in this population.

The regimens were generally well tolerated; 2 subjects discontinued study drug due to an AE.

Treatment-emergent AEs reported for ≥ 10.0% of all subjects were asthenia, fatigue, headache, anemia, pruritus, and nausea. The majority of events in all treatment groups were mild or moderate in severity. One death was reported approximately 33 weeks after completion of 16 weeks of study drug treatment that was deemed not associated with study drug treatment. The overall incidence of SAEs was low, with 1 SAE considered associated with DAAs; this AE (hepatotoxicity) led to discontinuation of study drug.

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