Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-450, ritonavir, ABT-267, ABT-333, ribavirin		
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,14,15,16,16a-tetradecahydrocyclopropa[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-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 ABT-333: (sodium N-{6-[3-tert-butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl]naphthalen-2-yl}methanesulfonamide hydrate) Ribavirin: 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide		

Title of Study: A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection (PEARL-III)

Investigator: Peter Ferenci, MD

Study Sites: 50 investigative sites in Austria, Belgium, Spain, Hungary, Israel, Italy, Poland, Portugal, Romania, Russian Federation, and the United States

Publications: 2

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 11 December 2012 Last Subject Last Visit: 19 August 2014	

Objectives:

The primary objectives of this study were to compare the safety of the combination of ABT-450/r/ABT-267 and ABT-333 administered with and without RBV for 12 weeks and to show the noninferiority in SVR_{12} rates (the percentage of subjects achieving a 12-week sustained virologic response [SVR] [HCV ribonucleic acid {RNA} < lower limit of quantitation {LLOQ} 12 weeks following therapy]) of 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 administered with and without RBV compared with the historical SVR rate of telaprevir plus pegylated interferon (pegIFN) and RBV therapy in treatment-naïve HCV subgenotype 1b-infected adults without cirrhosis.

The secondary objectives of this study were:

- to demonstrate the noninferiority in SVR_{12} rates of 12 weeks of treatment with ABT-450/r/ ABT-267 and ABT-333 without RBV to 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 with RBV;
- to compare the percentage of subjects with a decrease in hemoglobin to below the lower limit of normal (LLN) at the end of treatment between treatment arms;
- to show the superiority in SVR_{12} rates of 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 with and without RBV to the historical SVR rate of telaprevir plus pegIFN and RBV therapy; and
- to summarize the percentage of subjects with virologic failure during treatment and the percentage of subjects with relapse post-treatment in each treatment arm.

Methodology:

This was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the combination of ABT-450/r/ABT-267 and ABT-333 with and without RBV in treatment-naïve HCV subgenotype 1b-infected adults without cirrhosis.

Approximately 400 HCV subgenotype 1b-infected treatment-naïve adults without cirrhosis were to be randomized to Arm A (3-DAA + RBV) and Arm B (3-DAA) in a 1:1 ratio at approximately 60 sites.

- Arm A: ABT-450/r/ABT-267 150/100/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) + RBV[a] for 12 weeks;

Methodology (Continued):

- Arm B: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + placebo for RBV[a] for 12 weeks.

  a. RBV weight based, 1,000 mg to 1,200 mg daily divided BID per local label (e.g., < 75 kg = 1,000 mg daily divided BID or ≥ 75 kg = 1,200 mg daily divided BID).

The duration of the study was up to 60 weeks (not including a screening period of up to 35 days) consisting of the Treatment Period and the Post-Treatment Period.

In the Treatment Period, randomization was stratified by interleukin 28 B (IL28B) genotype (CC versus non-CC), and subjects received 12 weeks of therapy. In the Post-Treatment Period, all subjects administered at least 1 dose of study drug were to be followed for 48 weeks to monitor for safety, HCV RNA, the emergence and/or persistence of resistant viral variants, and assessment of patient-reported outcomes (PROs).

The primary analysis occurred after all subjects reached SVR_{12} or prematurely discontinued the study. Safety and efficacy evaluations occurred throughout the study by a Data Monitoring Committee.

Number of Subjects (Planned and Analyzed):

Approximately 400 subjects were planned to be enrolled; 419 subjects (210 in Arm A and 209 in Arm B) were enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV subgenotype 1b-infected, treatment-naïve adults (18 to 70 years of age, inclusive), with a body mass index (BMI) ≥ 18 to < 38 kg/m^2. Females were either postmenopausal for at least 2 years, surgically sterile, or of childbearing potential and practicing 2 effective forms of birth control while receiving study drug or sexually active with female partners only. Males must have been surgically sterile or agreed to practice 2 effective methods of birth control throughout the course of the study or sexually active with male partners only. Subjects had a chronic HCV genotype 1b infection, a plasma HCV RNA > 10,000 IU/mL, a liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis (e.g., a Metavir score of 3 or less or an Ishak score of 4 or less) or FibroTest® score ≤ 0.72 and aspartate aminotransferase (AST) to platelet ratio index ≤ 2, or FibroScan® result < 9.6 kPa.

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

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
ABT-450/ Ritonavir/ ABT-267	Abbott/AbbVie	Oral	Tablet	75/50/12.5 mg	12-006474
ABT-333	Abbott/AbbVie	Oral	Tablet	250 mg	12-004533
Ribavirin (US Ribasphere)	Tablets: Kadmon Pharmaceuticals, LLC[a] Capsules: [redacted] for Abbott/AbbVie	Oral	Capsule	200 mg	12-006205
Placebo for Ribasphere	Abbott/AbbVie	Oral	Capsule	0 mg	10-004370
Ribavirin (EU Copegus)	Tablets: Roche[a] Capsules: [redacted] for Abbott/AbbVie	Oral	Capsule	200 mg	12-005106 12-005107 12-005494
Placebo for Copegus	Abbott/AbbVie	Oral	Capsule	0 mg	12-002308

US = United States; EU = European Union

a. During the course of the study, DSM Pharmaceuticals Inc. manufactured for Three Rivers Pharmaceuticals, LLC and for Kadmon Pharmaceuticals, LLC. Kadmon Pharmaceuticals, LLC acquired Three River Pharmaceuticals. Ribavirin tablets used in lots 12-005106, 12-005107, and 12-005494 were manufactured by Roche. Tablets used in lot 12-006205 were manufactured by Kadmon Pharmaceuticals, LLC.

Duration of Treatment: Subjects received ABT-450/r/ABT-267 and ABT-333 with or without RBV for 12 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 evaluated at all Treatment Period Visits and at all Post-Treatment Visits (through 48 weeks after completion of treatment).

Criteria for Evaluation (Continued)

Resistance:

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

Patient-Reported Outcomes:

The change in functional wellbeing was 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). General Health Related Quality of Life (HRQoL) was assessed using the Short Form 36 version 2 (SF-36v2) non-disease specific HRQoL instrument.

Pharmacokinetic:

Individual plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, and RBV were determined for each subject at each study visit.

Safety:

The following safety evaluations were performed during the study: adverse event monitoring and vital signs, physical examination, electrocardiogram (ECG), and laboratory tests assessments.

Statistical Methods

Efficacy:

In order to control the Type I error rate, a fixed-sequence testing procedure was used to proceed through the primary and secondary endpoints in the order numbered below.

The primary efficacy endpoints were:

1. SVR_{12}: noninferiority of the 3-direct-acting antiviral agent (DAA) regimen to the historical SVR rate for telaprevir plus pegIFN and RBV therapy – lower confidence bound (LCB) of 2-sided 95% confidence interval (CI) for the percentage of subjects with SVR_{12} in the 3-DAA treatment group must have exceeded 73% to achieve noninferiority.
2. SVR_{12}: noninferiority of the 3-DAA + RBV regimen to the historical SVR rate for telaprevir plus pegIFN and RBV therapy – LCB for the percentage of subjects with SVR_{12} in the 3-DAA + RBV treatment group must have exceeded 73% to achieve noninferiority.

To test the hypothesis that the percentage of subjects in either treatment group who achieved SVR_{12} was noninferior to the historical SVR rate for telaprevir plus pegIFN and RBV therapy in the corresponding population, the simple percentage of subjects with SVR_{12} was calculated for each arm, and a 2-sided 95% CI was calculated using the normal approximation to the binomial distribution. In addition, a 2-sided 95% confidence interval for a SVR_{12} rate of 100% will also be calculated using Wilson score method for the single proportion. The lower bound of the 2-sided 95% CI must have been greater than 73% for a treatment group to be a success for the primary endpoint.

The secondary efficacy endpoints included in the fixed-sequence testing procedure were:

1. SVR_{12}: 3-DAA regimen noninferior to 3-DAA + RBV regimen using a 10.5% noninferiority margin.

Statistical Methods (Continued)

Efficacy (Continued):

2. Comparison of the percentage of subjects with a decrease in hemoglobin to below the LLN at the end of treatment with ABT-450/r/ABT-267 and ABT-333 with RBV versus without RBV.
3. SVR_{12}: Superiority of the 3-DAA + RBV regimen to the historical SVR rate for telaprevir plus pegIFN and RBV therapy – LCB must have exceeded 84% to achieve superiority.
4. SVR_{12}: Superiority of the 3-DAA regimen to the historical SVR rate for telaprevir plus pegIFN and RBV therapy – LCB must have exceeded 84% to achieve superiority.

To test the hypothesis that the percentage of subjects who achieved SVR_{12} in the 3-DAA treatment group was noninferior to the 3-DAA + RBV treatment group, the simple percentage of subjects with SVR_{12} was calculated for each group, and a 2-sided 95% CI for the difference in SVR_{12} rates (3-DAA minus 3-DAA + RBV) was calculated using the normal approximation to the binomial distribution. If the lower bound of the 2-sided 95% CI for the difference was above the noninferiority margin of –10.5%, the 3-DAA regimen was considered noninferior to the 3-DAA + RBV regimen.

To test the hypothesis that the percentage of subjects with a decrease in hemoglobin to below the LLN at the end of treatment was different between treatment groups, the differences between groups were analyzed using Fisher's exact test.

To test the hypotheses that the percentage of subjects in either treatment group who achieved SVR_{12} was superior to the historical SVR rate for telaprevir plus pegIFN and RBV therapy in the corresponding population, the simple percentage of subjects with SVR_{12} for each treatment group was calculated, and a 2-sided 95% CI was calculated using the normal approximation to the binomial. In addition, a 2-sided 95% confidence interval for a SVR_{12} rate of 100% will also be calculated using Wilson score method. The lower bound of the 2-sided 95% CI must have been greater than 84% for a treatment group to be a success for this endpoint.

Other secondary endpoints not included in the fixed sequence were:

- The percentage of subjects in each treatment group with on-treatment virologic failure during treatment (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 $\log_{10}$ IU/mL above nadir] at any time point during treatment or HCV RNA ≥ LLOQ persistently during treatment with at least 6 weeks [≥ 36 days] of treatment).
- The percentage of subjects in each treatment group with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment).

The simple percentages and 2-sided 95% CIs using the normal approximation to the binomial distribution of the subjects with virologic failure during treatment and post-treatment relapse were calculated and summarized. In addition, a 2-sided 95% confidence interval for a virologic failure or relapse rate of 0% will also be calculated using Wilson score method. These endpoints were not part of the fixed-sequence testing procedure as no hypothesis was being tested.

Interim analyses were conducted to evaluate futility. If rates of virologic breakthrough or post-treatment relapse were too high in the RBV-free group, enrollment was to be stopped and subjects in the RBV-free group who were still in the Treatment Period were to be offered open-label RBV.

Statistical Methods (Continued)

Resistance:

The following resistance information was analyzed for subjects receiving study drugs who did not achieve SVR and were in the primary virologic failure (PVF) population: 1) the variants at signature resistance-associated amino acid positions at baseline identified by population nucleotide sequencing were compared with the appropriate prototypic reference sequence, 2) the variants at available postbaseline time points identified by population and/or clonal nucleotide sequencing were compared to baseline and the appropriate prototypic reference sequences, 3) the most prevalent amino acid variants found by population sequencing and amino acid variants that emerged or became enriched in isolates from at least 2 subjects of the same subgenotype were summarized, and 4) the persistence of viral resistance was summarized for all subjects not achieving SVR, regardless of the reason.

Patient-Reported Outcomes:

Exploratory analyses of PROs were performed.

Summary statistics (n, mean, standard deviation, median, minimum, and maximum) at each visit and for change from baseline to each visit by treatment group were provided for the HCV-PRO total score, the EQ-5D-5L health index and Visual Analog Scale (VAS) scores, and the SF-36v2 Physical Component Summary and Mental Component Summary scores. For each of these scores, mean change from baseline to final treatment visit was compared between treatment groups using an analysis of covariance model with treatment group as a factor and baseline score as a covariate.

For HCV-PRO total score, a continuous plot by treatment group was provided with change from baseline on the horizontal axis and the cumulative percent of subjects experiencing up to that change on the vertical axis. These plots were used to display change from baseline to final treatment visit, for example.

In addition, the minimally important difference (MID) during treatment was determined for the HCV-PRO total score through receiver operating characteristic analysis by using a 5-point decrease from baseline to final treatment visit in SF-36v2 Mental Component Summary and Physical Component Summary scores as anchors. The percentage of subjects with a decrease from baseline to final treatment visit in the HCV-PRO total score > MID was compared between treatment groups using chi-square or Fisher's exact test.

Pharmacokinetic:

Plasma concentrations of ABT-450, ABT-267, ABT-333, ABT-333 M1 metabolite, ritonavir, and RBV were tabulated for each subject and group. Summary statistics were computed for each time and visit. Individual plasma concentrations were tabulated in relation to time of the last drug dose and summarized.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events were defined as any event that began or worsened in severity after initiation of study drug through 30 days after the last dose of study drug. The number and percentage of subjects in each treatment group with treatment-emergent adverse events were tabulated by primary MedDRA system organ class and preferred term and compared between treatment groups using Fisher's exact test. The tabulation of the number of subjects with treatment-emergent adverse events was also provided by severity rating and relationship to study drug.

Statistical Methods (Continued)

Safety (Continued):

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 postbaseline shifts in clinical laboratory values from low/normal to high and high/normal to low based on the normal range were summarized by treatment group.

In addition, the number and percentage of subjects with post-baseline values meeting prespecified criteria for potentially clinically significant (PCS) laboratory values were summarized by treatment group. Comparisons were performed between treatment groups of the percentage of subjects with PCS laboratory values for each parameter using Fisher's exact test.

Summary/Conclusions

Efficacy Results:

Subjects were administered the 3-DAA regimen of ABT-450/r/ABT-267 + ABT-333 with and without RBV for 12 weeks. HCV RNA levels were monitored for 48 weeks after the last dose of study drug.

Sustained virologic response 12 weeks postdosing was achieved by 209/210 (99.5%) subjects in the 3-DAA + RBV treatment group (95% CI: 98.6% – 100.0%) and by 209/209 (100.0%) subjects in the 3-DAA treatment group (95% CI: 98.2% – 100.0%). The LCB was above 73% (noninferiority threshold) for both treatment groups. Therefore, both primary endpoints were achieved, and both regimens demonstrated noninferiority to the historical control rate for therapy based on telaprevir plus pegIFN and RBV. In the 3-DAA + RBV treatment group, 1 (0.5%) subject experienced on-treatment virologic failure, and no subject experienced relapse by Post-Treatment Week 12. In the 3-DAA treatment group, no virologic failure was observed.

Sensitivity analyses that evaluated alternative methods to impute missing post-treatment virologic results were consistent with the primary analysis. A test of heterogeneity within each treatment group indicated no significant heterogeneity ($P = 0.606$ within the 3-DAA + RBV treatment group) across the 2 randomization strata defined by IL28B (CC versus non-CC). For each treatment group, the SVR_{12} rate was above the prespecified noninferiority threshold of 73% for all subgroups. When the 95% CI was calculated, the LCB was also above the noninferiority threshold. The LCB of the treatment group difference (when calculated) was above the prespecified noninferiority margin for 3-DAA versus 3-DAA + RBV for all subgroups.

The second secondary endpoint was analyzed with the following results:

The percentage of subjects with a decrease in hemoglobin to below the LLN at the end of treatment was statistically significantly lower in the 3-DAA treatment group (3.4%) than in the 3-DAA + RBV treatment group (51.2%) among subjects with hemoglobin ≥ LLN at baseline. The remaining 3 secondary endpoints were achieved:

- The SVR_{12} rate for the 3-DAA regimen was shown to be noninferior to the SVR_{12} rate for the 3-DAA + RBV regimen (lower bound of the 95% CI of –0.5% was above the prespecified noninferiority margin of –10.5%);
- For the 3-DAA + RBV regimen, the lower bound of the 95% CI for SVR_{12} of 98.6% was above the prespecified threshold of 84%, demonstrating superiority to the historical SVR rate for telaprevir plus pegIFN and RBV therapy (LCB must have exceeded 84% to achieve superiority);

Summary/Conclusions (Continued)

Efficacy Results (Continued):

- For the 3-DAA regimen, the lower bound of the 95% CI for SVR_{12} of 98.2% was above the prespecified threshold of 84%, demonstrating superiority to the historical SVR rate for telaprevir plus pegIFN and RBV therapy (LCB must have exceeded 84% to achieve superiority).

Results for the additional efficacy endpoint for sustained virologic response 24 weeks postdosing were consistent with the primary efficacy results with 100% agreement between SVR_{12} and SVR_{24} in each treatment group.

In the 3-DAA + RBV treatment group, 1 (0.5%) subject relapsed at Post-Treatment Week 36. In the 3-DAA treatment group, no relapse was observed.

For treatment-naïve, HCV subgenotype 1b-infected adults without cirrhosis, both noninferiority and superiority of 3-DAA + RBV and 3-DAA to the historical control rate for telaprevir plus pegIFN and RBV therapy were demonstrated for SVR_{12}. The 3-DAA regimen was shown to be noninferior to the 3-DAA + RBV regimen for SVR_{12}, while the percentage of subjects with a decrease in hemoglobin to below the LLN at the end of treatment was statistically significantly higher in the 3-DAA + RBV treatment group than in the 3-DAA treatment group. Virologic failure (on-treatment rebound or post-treatment relapse) was observed in 2 subjects in the 3-DAA + RBV treatment group and no subject in the 3-DAA treatment group.

Resistance Results:

Resistance analyses of subjects in the PVF population included 2 subjects who were treated with the 3-DAA + RBV regimen. At baseline, resistance-associated variants were not detected in NS3 in either subject, 1 subject had Y93H in NS5A, and both subjects had C316 variants in NS5B. The number of virologic failures in this study was too small to identify pre-existing variants that might predispose subjects to treatment failure. Treatment-emergent variants D168V in NS3, Y93H in NS5A, and M414I in NS5B were each detected in 1 subject. At follow-up time points, NS3 D168V was not detected at Post-Treatment Week 48, while NS5A Y93H and NS5B M414I persisted through Post-Treatment Week 48.

Patient-Reported Outcomes Results:

The majority of subjects in both treatment groups experienced decreases (that did not meet criteria to be considered even of minimal importance) or increases from baseline in their HRQoL, function, and wellbeing (per SF-36v2 Mental Component Summary, Physical Component Summary, EQ-5D-5L health index score, and HCV-PRO total scores) at the end of treatment. Similar improvements from baseline mean were observed after treatment for both treatment groups. The addition of RBV to 3-DAA did not have a significant impact on subjects' HRQoL.

Pharmacokinetic Results:

Based on the binned C_{trough} values, the exposures achieved for ABT-450, ABT-267, ritonavir, ABT-333, and RBV in treatment-naïve, HCV subgenotype 1b-infected subjects were comparable to exposures achieved in the treatment-naïve HCV genotype 1-infected subjects in Phase 3 Study M11-646 Arm A (< 20% difference). RBV dosing does not appear to affect the concentrations of the DAAs or ritonavir (≤ 21% difference).

Summary/Conclusions (Continued)

Safety Results:

The safety population included all randomized subjects who received at least 1 dose of study drug (N = 419).

ABT-450/r/ABT-267 and ABT-333 coadministered with and without RBV for 12 weeks to treatment-naïve HCV subgenotype 1b-infected adults without cirrhosis was well tolerated, as demonstrated by the low rate of study drug-related serious adverse events and the fact that no subject prematurely discontinued study drug due to a treatment-emergent adverse event. While most subjects experienced at least 1 adverse event during the Treatment Period, most of these adverse events were mild in severity.

The most common treatment-emergent adverse events were headache, fatigue, pruritus, nausea, and asthenia in the 3-DAA + RBV treatment group and headache and fatigue in the 3-DAA treatment group. These adverse events were comparable in nature and frequency to those reported in another study utilizing the 3-DAA ± RBV regimen. Pruritus (11.9% versus 5.3%), nausea (11.0% versus 4.3%), insomnia (9.0% versus 3.3%), cough (9.0% versus 2.4%), and anemia (6.7% versus 0.5%) occurred statistically significantly more frequently in the 3-DAA + RBV treatment group compared with the 3-DAA treatment group. These adverse events are all consistent with the known safety profile of RBV. Among the adverse events of interest, when compared with the 3-DAA + RBV treatment group, the 3-DAA treatment group had a lower frequency of bilirubin-related adverse events (1.0% versus 5.7%), rash-related events (10.5% versus 17.1%), and anemia-related adverse events (0.5% versus 8.6%) based on SMQ/CMQ search criteria, suggesting RBV may have contributed to the occurrence of some of these events. These events were generally assessed as mild in severity.

No deaths were reported. Eight subjects (4 in each treatment group) experienced treatment-emergent serious adverse events during the Treatment Period. None of these events was assessed by the investigator or AbbVie to have a reasonable possibility of relationship to study drug, with the exception of 1 event of arthritis in the 3-DAA treatment group. No commonality was evident among the reported events and all these subjects achieved SVR_{12}. One subject in the 3-DAA treatment group experienced a serious adverse event of spontaneous abortion at approximately 8 weeks of gestation during the Post-Treatment Period (135 days after last dose of study drug) that was considered by the investigator as having a reasonable possibility of being related to DAA treatment.

Review of the specific MedDRA search queries for rash revealed that events of rash and pruritus were more frequent when RBV was included in the regimen. The events reported both in the 3-DAA + RBV and 3-DAA treatment groups were mainly mild and did not result in treatment interruption or discontinuation. There were no serious skin events.

Summary/Conclusions (Continued)

Safety Results (Continued):

Analysis of hematology parameters showed statistically significant differences in the mean change from baseline to the Final Treatment Visit in hemoglobin, hematocrit, red blood cell, reticulocytes, platelet count, WBCs, lymphocytes, monocytes, eosinophils, and basophils; however, most of these mean changes were small, and no more than 2 subjects in either treatment group experienced a PCS value for any hematology parameter. The mean decrease in hemoglobin was 17.2 g/L greater in the 3-DAA + RBV treatment group than in the 3-DAA treatment group. In fact, the mean change from baseline in hemoglobin for the 3-DAA group (mean hemoglobin of 142.4 g/L at baseline to 136.7 g/L at the Final Treatment Visit) suggested little or no impact on hemoglobin when RBV was not part of the DAA regimen. One subject in the 3-DAA + RBV treatment group experienced a grade 3 reduction in hemoglobin. The differential rates of abnormalities in hemoglobin, hematocrit, and reticulocytes are consistent with the known hemolytic anemia associated with RBV. The only hematology parameter with a statistically significant difference in mean change from baseline to the Final Post-Treatment Visit was activated partial thromboplastin time (APTT); however, the number of subjects with a final post-treatment value was small (N = 11 for each treatment group) and the changes were small and not clinically meaningful.

Analysis of chemistry parameters showed small but statistically significant differences in mean change from baseline to Final Treatment Visit between treatment groups in calculated creatinine clearance, uric acid, calcium, magnesium, chloride, bicarbonate, glucose, total protein, cholesterol, and triglycerides. PCS values for chemistry parameters were infrequent, occurring in no more than 3 subjects in either treatment group, with the exception of total bilirubin.

For total bilirubin, statistically significant differences between treatment groups in mean change from baseline were observed at all time points during treatment. In the 3-DAA + RBV treatment group, 5.7% of subjects had at least a grade 3 postbaseline total bilirubin compared with 0.5% of subjects in the 3-DAA treatment group. This suggests that the effect of ABT-450 on serum bilirubin levels due to inhibition of bilirubin transporters is substantially augmented by RBV-associated hemolysis.

Mean decreases from baseline were observed in ALT and AST at the Final Treatment Visit, the Post-Treatment Week 4 Visit, and the Final Post-Treatment Visit, which were similar in both treatment groups. Two subjects in the 3-DAA + RBV treatment group experienced postbaseline transient elevations in ALT to > 5 × ULN, which improved without study drug interruption or discontinuation. The hepatic panel did not consider these cases to be consistent with Hy's law.

There were no statistically significant differences in mean change from baseline to Final Post-Treatment Visit for any chemistry parameter.

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

In summary, adverse event and laboratory safety data in this study demonstrate that both the 3-DAA regimen and the 3-DAA + RBV regimen are well tolerated; however, the 3-DAA regimen without RBV was associated with lower rates of RBV-associated events, such as anemia, rash, and hyperbilirubinemia.

Safety Results (Continued):

Conclusions:

A 12-week regimen of ABT-450/r/ABT-267 and ABT-333 ± RBV in treatment-naïve HCV subgenotype 1b-infected adults without cirrhosis showed an SVR_{12} of 99.5% with RBV and 100.0% without RBV. Both treatment regimens demonstrated noninferiority and superiority to the historical control rate for telaprevir plus pegIFN and RBV in HCV genotype 1b-infected adults without cirrhosis. The SVR_{12} rate for the 3-DAA regimen was noninferior to the SVR_{12} rate for the 3-DAA + RBV regimen. Two subjects in the 3-DAA + RBV treatment group and no subject in the 3-DAA treatment group experienced virologic failure during treatment or post-treatment. The 12-week regimen of ABT-450/r/ABT-267 and ABT-333 ± RBV was well tolerated, with no subject prematurely discontinuing study drug because of a treatment-emergent adverse event. The adverse events observed in this study were generally consistent with those demonstrated for the combination of 3 DAAs with RBV in previous studies. Adverse events historically associated with RBV were less frequent in subjects who received 3 DAAs without RBV. Taken together, the findings from this study indicate that the 3-DAA regimen should be used without RBV in treatment-naïve genotype 1b-infected adults without cirrhosis.

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