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-1*H*-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 1a Chronic Hepatitis C Virus (HCV) Infection (PEARL-IV)		
Investigator: David Bernstein, MD		
Study Sites: 53 investigative sites in United States, Canada, and the United Kingdom		
Publications: 3		

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 14 March 2013 Last Subject Last Visit: 07 September 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 1a-infected adults without cirrhosis.

The secondary objectives of this study were:

- to compare the percentage of subjects with a decrease in hemoglobin from at or above the lower limit of normal (LLN) to below the 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;
- 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; 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 1a-infected adults without cirrhosis.

Approximately 300 HCV subgenotype 1a-infected treatment-naïve adults without cirrhosis were to be randomized to Arm A and Arm B in a 1:2 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 (N = 100);
- Arm B: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + placebo for RBV[a] for 12 weeks (N = 200).

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 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).

Methodology (Continued):

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 300 subjects were planned to be enrolled; 305 subjects (100 in Arm A and 205 in Arm B) were enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV subgenotype 1a-infected, treatment-naïve adults (18 to 70 years of age, inclusive), with a body mass index ≥ 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 1a 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/r/ABT-267	AbbVie	Oral	Tablet	75/50/12.5 mg	12-005439
ABT-333	AbbVie	Oral	Tablet	250 mg	12-005683
RBV capsules (US Ribasphere®)	Overencapsulated by: [redacted] for AbbVie[a]	Oral	Capsule	200 mg	12-006205
Placebo for overencapsulated RBV	AbbVie	Oral	Capsule	0 mg	12-002605 10-004358 12-002308
RBV capsules (EU Copegus®)	Overencapsulated by: [redacted] for AbbVie[a]	Oral	Capsule	200 mg	12-003233

EU = European Union; RBV = ribavirin; US = United States

a. Ribavirin tablets were commercial product. RBV tablets used in overencapsulated lots 12-003233 and 12-002308were manufactured by Roche Pharma AG. Ribavirin tablets used in overencapsulated lot 12-006205 were manufactured by Kadmon Pharmaceuticals, LLC.

Note: 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 Rivers Pharmaceuticals.

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).

Resistance:

For subjects who received active drugs and did not achieve SVR: the variants at 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 clonal nucleotide 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 functional wellbeing was assessed using the HCV Patient-Reported Outcomes Instrument (HCV-PRO). 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 health survey (SF-36v2) non-disease specific HRQoL instrument.

Pharmacokinetic:

Plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, and ribavirin (RBV) (Arm A only) were determined in samples harvested at each study visit; the time of the last dose of study drug was also recorded.

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:

To control for 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 65% 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 65% to achieve noninferiority.

Statistical Methods (Continued)

Efficacy (Continued):

To evaluate whether 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, and a 2-sided 95% CI was calculated using the normal approximation to the binomial distribution. The lower bound of the 2-sided 95% CI must have been greater than 65% in order 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. 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.
2. 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 75% to achieve superiority.
3. SVR_{12}: Superiority of the 3-DAA regimen to the historical SVR rate for telaprevir plus pegIFN and RBV therapy – LCB must have exceeded 75% to achieve superiority.
4. SVR_{12}: the 3-DAA regimen noninferior to the 3-DAA + RBV regimen using a 10.5% noninferiority margin.

To evaluate whether the percentage of subjects with a decrease in hemoglobin from at or above the LLN 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 evaluate whether 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. The lower bound of the 2-sided 95% CI must have been greater than 75% in order for a regimen to be a success.

To evaluate whether 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.

Other secondary endpoints not included in the fixed sequence were:

1. 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).
2. 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 of study drugs among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment).

Statistical Methods

Efficacy (Continued):

The 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. 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.

Resistance:

The following resistance information was analyzed for subjects receiving study drugs who did not achieve SVR: 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 with 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 for all subjects not achieving SVR, 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 Analogue 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 the HCV-PRO total score, a continuous plot by treatment group was provided with change from baseline on the horizontal axis and the cumulative percentage 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:

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

Population pharmacokinetic analyses were performed using the actual sampling time relative to dosing. Pharmacokinetic models were built using a non-linear mixed-effect modeling approach.

Statistical Methods (Continued)

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.

Laboratory data values were categorized as low, normal, or high based on reference ranges of the laboratory used in this study. The number and percentage 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 postbaseline 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:

Sustained virologic response 12 weeks postdosing was achieved by 97/100 (97.0%) subjects in the 3-DAA + RBV treatment group (95% CI: 93.7% to 100.0%) and by 185/205 (90.2%) subjects in the 3-DAA treatment group (95% CI: 86.2% to 94.3%). The LCB was above 65% (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 (1.0%) subject experienced on-treatment virologic failure and 1 (1.0%) subject experienced relapse by Post-Treatment Week 12, for a total of 2.0% virologic failures. In the 3-DAA treatment group, 6 (2.9%) subjects experienced on-treatment virologic failure and 10 (5.2%) subjects experienced relapse by Post-Treatment Week 12, for a total of 7.8% virologic failures.

The first 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 (3.9%) than in the 3-DAA + RBV treatment group (42.0%) among subjects with hemoglobin $\geq$ LLN at baseline. The next 2 ranked secondary endpoints were achieved, but the final ranked secondary endpoint was not achieved:

Summary/Conclusions (Continued)

Efficacy Results (Continued):

- For the 3-DAA + RBV treatment group, the lower bound of the 95% CI for SVR_{12} of 93.7% was above the prespecified threshold of 75%, demonstrating superiority to the historical SVR rate for telaprevir plus pegIFN and RBV therapy;
- For the 3-DAA treatment group, the lower bound of the 95% CI for SVR_{12} of 86.2% was above the prespecified threshold of 75%, demonstrating superiority to the historical SVR rate for telaprevir plus pegIFN and RBV therapy;
- The SVR_{12} rate for the 3-DAA treatment group was not shown to be noninferior to the SVR_{12} rate for the 3-DAA + RBV treatment group (lower bound of the 95% CI for the treatment difference of SVR_{12} was –12.0% and therefore was below the prespecified noninferiority margin of –10.5%). In addition, the upper bound of the CI did not cross zero, indicating a statistically significant difference between treatment groups at the nominal 0.05 level.

In subgroup analyses, for each treatment group, the SVR_{12} rate was above the prespecified noninferiority threshold of 65% for all subgroups. While some differences in response rates across subgroups were observed in various analyses, these were generally small and not considered clinically significant.

Results for the additional efficacy endpoint of sustained virologic response 24 weeks postdosing were consistent with the primary efficacy results with 98% agreement between SVR_{12} and SVR_{24} in each treatment group.

One (1.0%) subject relapsed in the 3-DAA + RBV treatment group. In the 3-DAA treatment group, 14 (7.2%) subjects relapsed post-treatment: 10 during the SVR_4 window, 3 during the SVR_{24} window, and 1 after the SVR_{24} assessment window.

Overall, virologic failure (on-treatment rebound or post-treatment relapse) was observed in 2 (2.0%) subjects in the 3-DAA + RBV treatment group and 20 (9.8%) subjects in the 3-DAA treatment group.

Resistance Results:

Resistance analyses of the PVF population included 22 subjects: 2 subjects in the 3-DAA + RBV treatment group and 20 subjects in the 3-DAA treatment group. In the 3-DAA treatment group, the presence of Q80K at baseline was more common among subjects in the PVF population (13/20 [65%]) compared with the matched set of subjects who achieved SVR_{12} (8/29 [27.6%]; $P = 0.018$ for the difference). In the 3 DAA + RBV treatment group, Q80K was present in 1 of 2 virologic failures, a prevalence similar to that expected in the general HCV genotype 1a (GT1a)-infected population. This, combined with the high SVR rate observed in the 3-DAA + RBV treatment group, suggests that Q80K had minimal impact on SVR rate in these subjects. There was no apparent association between treatment outcome in the 3-DAA + RBV treatment group and other baseline variants at signature resistance-associated amino acid positions.

The predominant variants in the subjects in the PVF population at the time of failure were Y56H, R155K, D168A, D168H, and D168V in NS3; M28T, M28V, Q30E, Q30R, and H58D in NS5A; and S556G in NS5B. Of the 22 subjects in the PVF population, all had resistance-associated variants in at least 1 target and 13 had resistance-associated variants in all 3 targets at the time of failure. The single subject who prematurely discontinued treatment and had sequence data available had pre-existing Q80K in NS3 but had no resistance-associated variants in NS3, NS5A, or NS5B at the time of treatment discontinuation.

Summary/Conclusions (Continued)

Resistance Results (Continued):

Treatment-emergent resistance-associated variants were observed in NS3, NS5A, and NS5B in 21, 18, and 13 of the 22 subjects in the PVF population, respectively. Variants in NS3 declined through Post-Treatment Week 24 (8/16, 50%) and Post-Treatment Week 48 (2/16, 12.5%). Treatment-emergent resistance-associated variants in NS5A and NS5B remained detectable at similar levels through Post-Treatment Week 48.

Patient-Reported Outcomes Results:

More than half of subjects in both treatment groups experienced either 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, 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 at the end of the study.

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 1a-infected subjects without cirrhosis in the present study are comparable (< 25% difference) with exposures achieved in the treatment-naïve HCV genotype 1-infected subjects in Phase 3 Study M11-646 (Arm A). RBV dosing does not appear to affect the concentrations of the DAAs or ritonavir (≤ 26% difference).

Safety Results:

The safety population included all randomized subjects who received at least 1 dose of 3-DAA study drug (N = 305).

ABT-450/r/ABT-267 and ABT-333 coadministered with and without RBV for 12 weeks to treatment-naïve HCV subgenotype 1a-infected adults without cirrhosis was well tolerated, as evidenced by the low rate of subjects prematurely discontinuing study drug due to a treatment-emergent adverse event (< 1%). While the majority of subjects experienced at least 1 adverse event during the Treatment Period, most of these adverse events were mild in severity, with few severe or serious adverse events.

The most common treatment-emergent adverse events were diarrhea, fatigue, headache, insomnia, nausea, and pruritus in the 3-DAA + RBV treatment group and diarrhea, fatigue, headache, and nausea 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. Of the treatment-emergent adverse events reported for ≥ 5.0% of subjects in either treatment group, insomnia (17.0% versus 7.8%), arthralgia (9.0% versus 2.4%), dyspnea exertional (7.0% versus 0.5%), blood bilirubin increased (7.0% versus 0%), dry skin (6.0% versus 1.0%), and anemia (6.0% versus 0%) occurred statistically significantly more frequently ($P \leq 0.05$) in the 3-DAA + RBV treatment group, and memory impairment (6.8% versus 1.0%) occurred statistically significantly more frequently in the 3-DAA treatment group. Most of the adverse events occurring with greater frequency in the 3-DAA + RBV treatment group are consistent with the known safety profile of RBV. Similarly, when compared with the 3-DAA + RBV treatment group, the 3-DAA treatment group had a lower frequency of rash-related adverse events (17.6% versus 26.0%) and anemia-related adverse events (0.5% versus 9.0%), suggesting a causal or potentiating role for RBV.

Summary/Conclusions (Continued)

Safety Results (Continued):

One subject in the 3-DAA group died due to a non-treatment-emergent adverse event of brain death approximately 7 months after taking her last doses of study drug. The investigator considered the fatal event as having no reasonable possibility of being related to study drugs and more likely due to anoxic brain damage. Three (3.0%) subjects in the 3-DAA + RBV treatment group and 1 (0.5%) subject in the 3-DAA treatment group experienced treatment-emergent serious adverse events. No specific serious adverse event (preferred term) was reported for more than 1 subject, and no commonality was suggested. One of the 4 serious adverse events (pancreatitis in a subject with a past history of pancreatitis) was considered to have a reasonable possibly of relationship to DAA or RBV treatment; this event resolved after 16 days and did not result in study drug interruption or discontinuation.

Two (1.0%) subjects in the 3-DAA treatment group experienced adverse events that led to premature discontinuation of study drug (diverticulitis and drug abuse), neither of which was considered to have a reasonable possibility of relationship to DAA or RBV.

Consistent with the known hemolytic effect of RBV, the 3-DAA + RBV treatment group had greater decreases in hemoglobin, hematocrit, and red blood cell counts and greater increases in reticulocyte counts than the 3-DAA treatment group at all time points. Differences were also observed in APTT, basophils, eosinophils, INR, lymphocytes, monocytes, platelets, and prothrombin time, but these changes were small and not clinically meaningful. One subject in the 3-DAA + RBV treatment group experienced a postbaseline decreased hemoglobin value of grade 3 or higher; this subject received a blood transfusion. The mean hemoglobin value for the 3 DAA + RBV treatment group decreased from 147.2 g/L at baseline to 126.4 g/L at the Final Treatment Visit; a decrease that was 15.4 g/L greater than in the 3-DAA treatment group. The presence of a concomitant reticulocytosis confirms that the hemoglobin decrease is due to hemolysis, which is known to occur with RBV administration. These findings suggest administration of RBV with the 3-DAA regimen was better tolerated than previously reported in studies where RBV was used in combination with pegIFN.

Analysis of chemistry parameters showed small but statistically significant differences between treatment groups in mean change from baseline to the Final Treatment Visit in bicarbonate, calcium, cholesterol, inorganic phosphate, magnesium, triglycerides and uric acid. PCS values were infrequent, occurring in no more than 3 subjects in either treatment group for any chemistry parameter, with the exception of total bilirubin. There were no statistically significant differences between treatment groups in mean change from baseline to the Final Post-Treatment Visit for any chemistry parameter, with the exception of bicarbonate for which the mean changes from baseline at the Final Treatment Visit in both arms were small and not considered clinically meaningful.

Mean total bilirubin levels increased in both treatment groups from baseline to Week 1 and declined thereafter, driven primarily by increases in indirect bilirubin. This finding has been observed in previous studies of ABT-450/r and is consistent with the inhibitory action of ABT-450 on the transporter OATP1B1. Of note, mean bilirubin levels were significantly higher at all time points during treatment in the 3-DAA + RBV treatment group compared with the 3-DAA treatment group. In the 3-DAA + RBV treatment group, 3.0% of subjects experienced a total bilirubin elevation of grade 3 or higher, compared with 0.5% of subjects in the 3-DAA treatment group. These findings suggest that the frequency and magnitude of hyperbilirubinemia associated with ABT-450-containing regimens is significantly enhanced in the presence of RBV-induced hemolysis. There were no discontinuations or interruptions due to hyperbilirubinemia.

Summary/Conclusions (Continued)

Safety Results (Continued):

Mean decreases were observed in ALT, AST, and GGT at the Final Treatment Visit, Post-Treatment Week 4 Visit, and Final Post-Treatment Visit, which were similar in both groups and consistent with clearance of HCV from the liver. One subject in each treatment group experienced transient elevations in ALT to > 5 × ULN that resolved with continued study drug treatment. No cases consistent with Hy's law were identified.

No clinically meaningful results of urinalysis or vital signs were observed. One adverse event of abnormal ECG was reported, but no trends or patterns were noted to suggest an electrocardiographic safety signal.

Conclusions:

In treatment-naïve HCV subgenotype 1a-infected adults without cirrhosis, a 12-week regimen of ABT-450/r/ABT-267 and ABT-333 achieved an SVR_{12} rate of 97.0% when administered with RBV and 90.2% when administered without RBV. Both treatment regimens demonstrated noninferiority and superiority to the historical control rate for telaprevir plus pegIFN and RBV in the same population. The 3-DAA regimen did not demonstrate noninferiority to the 3-DAA + RBV regimen with regard to SVR_{12} rate. The 12-week regimen of ABT-450/r/ABT-267 and ABT-333 ± RBV was generally well tolerated, with only 2 subjects discontinuing study drug because of a treatment-emergent adverse event. Adverse events reported in this study were generally consistent with the established safety profile for RBV and those demonstrated for the combination of 3-DAAs with RBV in previous studies. Therefore, RBV appears to increase the clinical efficacy of this 3-DAA regimen in HCV genotype 1a-infected patients without cirrhosis. Based on the results of this study, the 3-DAA + RBV regimen for 12 weeks is recommended for noncirrhotic HCV subgenotype 1a-infected treatment-naïve patients. As the 3-DAA regimen achieved > 90% SVR_{12}, the 3-DAA regimen without RBV is proposed as an alternative based on a benefit/risk assessment for individual patients.

Date of Report: 23Apr2015