Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="2">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="2">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
ABT-450, ritonavir, ABT-267, ABT-333, ribavirin</td></tr>
<tr><td>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,14,15,16,16atetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate
ritonavir: 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-thiazolylmethylester, [5S-(5R*,8R*,10R*,11R*)]
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)
Ribavirin: 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide</td></tr>
<tr><td colspan="3">Title of Study: A Randomized, Open-Label, Multicenter Study to Evaluate the Safety and Antiviral Activity of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin in Treatment-Experienced Subjects With Genotype 1b Chronic Hepatitis C Virus (HCV) Infection (PEARL–II)</td></tr>
<tr><td colspan="3">Investigator: Pietro Andreone, MD</td></tr>
<tr><td colspan="3">Study Sites: 43 investigative sites in United States, Austria, Belgium, Italy, Portugal, Puerto Rico, Sweden, Switzerland, The Netherlands, and Turkey</td></tr>
</table>

Publications: 1	
Studied Period (Years): First Subject First Visit: 14 August 2012 Last Subject Last Visit: 13 October 2014	**Phase of Development:** 3

Objectives:

The primary objectives of this study were to evaluate the safety of 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 with and without ribavirin (RBV) and to show the noninferiority in SVR_{12} rates (the percentage of subjects achieving a 12-week sustained virologic response [SVR_{12}] [HCV RNA < lower limit of quantitation {LLOQ} 12 weeks following therapy]) in both arms to the historical SVR rate of telaprevir plus pegylated interferon (pegIFN) and RBV (pegIFN/RBV) therapy.

The secondary objectives of this study were: to compare the percentage of subjects with a decrease in hemoglobin to below the lower limit of normal (LLN) at the end of treatment with ABT-450/r/ABT-267 and ABT-333 with RBV and without RBV; 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 telaprevir plus pegIFN and RBV SVR rate; to show 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 post-treatment relapse in each of the treatment groups.

Methodology:

This was a Phase 3, open-label, randomized, multicenter study evaluating the combination regimen of ABT-450/r/ABT-267 and ABT-333 with and without RBV in pegIFN/RBV treatment-experienced, noncirrhotic, HCV subgenotype 1b (GT1b)-infected subjects.

Approximately 210 HCV GT1b-infected adults were to be randomized to Arm 1 (ABT-450/r/ABT-267, ABT-333, and RBV) and Arm 2 (ABT-450/r/ABT-267 and ABT-333) in a 1:1 ratio at approximately 45 sites. The treatment arms were:

- Arm 1: ABT-450/r/ABT-267 150/100/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) + weight-based RBV for 12 weeks;
- Arm 2: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID for 12 weeks

RBV dosing was weight-based, either 1,000 mg or 1,200 mg daily divided by 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 planned to be up to 60 weeks (not including a Screening Period of up to 35 days) consisting of a 12-week Treatment Period and a 48-week Post Treatment Period.

Subjects were stratified by the type of nonresponse to previous pegIFN/RBV treatment (null responders, nonresponders/partial responders, and relapsers). The number of nonresponders/partial responders plus relapsers enrolled across Arms 1 and 2 was limited to 130 to ensure that at least 80 null responders were enrolled. In addition, the relapsers were limited to 60 subjects (approximately 30% of all subjects enrolled).

Methodology (Continued):

The categories of treatment experience with pegIFN/RBV were defined as follows:

- Null-responders: received at least 12 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a 2 $\log_{10}$ international units (IU)/mL reduction in HCV RNA at Week 12. Subjects were considered to have met this definition if the lack of treatment response was documented following 10 to 16 weeks of treatment;
- Non-responders/partial responders: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved $\geq$ 2 $\log_{10}$ IU/mL reduction in HCV RNA at Week 12, but failed to achieve HCV RNA undetectable at the end of treatment. Subjects were considered to have met this definition if the lack of treatment response was documented following 10 to 16 weeks of treatment; or
- Relapsers: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up.

All subjects who received at least 1 dose of study drugs were to be monitored for safety, HCV RNA, the emergence and/or persistence of resistant viral variants, and assessment of patient-reported outcomes (PROs) for an additional 48 weeks following the last dose of study drugs.

The primary analysis occurred after all subjects completed the Post-Treatment Week 12 Visit or prematurely discontinued from study. For the primary analysis, the data were locked after performing appropriate data cleaning. Data after Post-Treatment Week 12 were added to a subsequent version of the database which were cleaned and locked at the end of the study.

Number of Subjects (Planned and Analyzed):

Approximately 210 subjects were planned to be enrolled; 187 subjects were randomized and 186 subjects (91 in Arm 1 and 95 in Arm 2) received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV-infected, treatment-experienced adults (18 to 70 years of age, inclusive), with a body mass index $\geq$ 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. Males must have been surgically sterile or agreed to practice 2 effective methods of birth control throughout the course of the study. Subjects had a chronic HCV GT1b 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 $\leq$ 0.72 and aspartate aminotransferase (AST) to platelet ratio index $\leq$ 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	Abbott/AbbVie	Oral	Tablet	75 mg/ 50 mg/ 12.5 mg	12-006474
ABT-333	Abbott/AbbVie	Oral	Tablet	250 mg	12-006334
Ribavirin	Roche or Kadmon Pharmaceuticals, LLC[a]	Oral	Tablet	200 mg	12-001669 12-005991 12-000489 12-001632 12-001631 12-006116
ABT-267	Abbott/AbbVie	Oral	Tablet	25 mg	11-002814
ABT-333	Abbott/AbbVie	Oral	Tablet	400 mg	11-005348
ABT-450	Abbott/AbbVie	Oral	Tablet	50 mg	11-005848
Ritonavir	Abbott/AbbVie	Oral	Capsule	100 mg	12-001426

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 Rivers Pharmaceuticals. Ribavirin tablets used in Lots 12-001669 and 12-005991 were manufactured at Kadmon Pharmaceuticals, LLC. Lots 12-000489, 12-001632, 12-001631, and 12-006116 were manufactured by Roche.

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 $\log_{10}$ IU/mL was assessed at all Treatment Period visits and at all post-treatment visits.

Resistance:

For subjects who received study drugs and did not achieve SVR, 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 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 disease-specific function and wellbeing were 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 Health Survey – Version 2 health survey (SF-36v2) non-disease specific HRQoL instrument.

Criteria for Evaluation (Continued)

Pharmacokinetic:

Plasma concentrations for ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, and RBV (Arm 1 only) were determined in samples harvested at each study visit for each subject and arm; the time of the last dose of study drug was also recorded.

Safety:

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

Statistical Methods

Efficacy:

All efficacy endpoints were analyzed using the intent-to-treat (ITT) GT1b efficacy subset. This subset was defined to include the ITT population with HCV GT1b infection who were assigned to and treated with ABT-450/r/ABT-267 coformulated drug.

Multiplicity was controlled across the primary and secondary endpoints using a fixed sequential testing procedure. The primary endpoints were:

1. noninferiority of Arm 2 to the historical control rate for telaprevir plus pegIFN/RBV (lower confidence bound [LCB] of the 2-sided 95% confidence interval [CI] for the percentage of subjects with SVR_{12} in Arm 2 must have exceeded 64% to achieve noninferiority); and
2. noninferiority of Arm 1 to the historical control rate for telaprevir plus pegIFN/RBV (LCB for the percentage of subjects with SVR_{12} in Arm 1 must have exceeded 64% to achieve noninferiority).

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. The 95% corrected CI using Wilson score method was obtained when the point estimate was 0% or 100%. The lower bound of the 2-sided 95% CI must have been greater than 64% in order for a treatment group to be a success for the primary endpoint.

Only if success was demonstrated for the primary endpoint of noninferiority in SVR_{12} rate of Arm 2 to the historical rate for telaprevir plus pegIFN and RBV therapy did the testing proceed to the second primary endpoint of noninferiority in SVR_{12} rate of Arm 1 to the historical rate for telaprevir plus pegIFN and RBV therapy.

The secondary efficacy endpoints included in the fixed-sequence 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 Arm 1 to the historical rate for telaprevir plus pegIFN/RBV – LCB must exceed 75% to achieve superiority.
3. SVR_{12}: Superiority of Arm 2 to the historical rate for telaprevir plus pegIFN/RBV – LCB must exceed 75% to achieve superiority.
4. SVR_{12}: Noninferiority of Arm 2 to Arm 1 using a –10.5% noninferiority margin.

Only if success was demonstrated for the second primary endpoint would testing have proceeded to the first secondary endpoint of percentage of subjects with a decrease in hemoglobin to below the LLN by the end of treatment with ABT-450/r/ABT-267 and ABT-333 with RBV versus without RBV. Similarly, testing proceeded through the other secondary endpoints only if success was met for the preceding endpoint.

Statistical Methods (Continued)

Efficacy (Continued):

Other secondary endpoints not included in the fixed sequence testing procedure were the percentage of subjects in each treatment group with virologic failure during treatment and the percentage of subjects in each treatment group with post-treatment relapse.

Resistance:

The following resistance information was analyzed for subjects 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 the change in non-disease-specific HRQoL, HCV-specific function and wellbeing, and health state utility were measured using the SF-36v2, HCV-PRO, and EQ-5D-5L instruments, respectively. SF-36v2 and HCV-PRO were analyzed by their component summary/total scores, as appropriate. The EQ-5D-5L was analyzed by utility score and by visual analogue scale (VAS) response. Change from baseline in the PRO summary measures was summarized and compared between arms using analysis of covariance models with arm as a factor and baseline score as a covariate.

The percentage of subjects without a decrease from baseline to the Final Treatment Visit that is greater than or equal to the minimally important difference (MID) for HCV-PRO total score, EQ-5D-5L health index, and SF-36v2 component summary scores were compared between arms. The MIDs for the HCV-PRO total score and the EQ-5D-5L health index are based on receiver operating characteristic curve anchored by SF-36v2 Mental Component Summary and SF-36v2 Physical Component Summary decrease of 5 points.

Pharmacokinetic:

Individual plasma concentrations of ABT-450, ritonavir, ABT-333, ABT-333 M1 metabolite, ABT-267, and RBV were tabulated in relation to time of the last drug dose and summarized.

Safety:

The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and preferred term for each treatment arm; comparisons were performed between the arms using Fisher's exact test. Tabulations were also provided in which the number of subjects reporting an adverse event (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 by arm and compared between arms using analysis of variance with treatment group as factor. Laboratory and vital sign values that were potentially clinically significant (PCS), according to predefined criteria, were identified and the percentage of subjects with PCS values during the Treatment Period was compared between arms using Fisher's exact tests.

Summary/Conclusions

Efficacy Results:

Subjects were administered the 3-direct-acting antiviral agent (DAA) regimen of ABT-450/r/ABT-267 + ABT-333 with or 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 86/88 (97.7%) subjects in the 3-DAA + RBV treatment group (95% CI: 94.6% – 100.0%) and by 91/91 (100%) subjects in the 3-DAA treatment group (95% CI: 95.9% – 100.0%). The LCB was above 64% (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.

Sensitivity analyses that evaluated alternative methods to impute missing post-treatment virologic results were consistent with the primary analysis. For the 3-DAA + RBV and 3-DAA treatment groups, no significant heterogeneity was observed across the randomization strata defined by response to previous pegIFN/RBV treatment (null responder, non/partial responder, relapser). Due to the very high overall response, the subgroup factors had no meaningful impact on SVR_{12} rates. For each treatment group, the SVR_{12} rate was above the prespecified noninferiority threshold of 64% for all subgroups. When the 95% CI could be calculated, the LCB was also above the noninferiority threshold for all subgroups.

Results of the secondary endpoints were as follows:

- 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 (42.0%) than in the 3-DAA treatment group (5.5%);
- For the 3-DAA + RBV treatment group, SVR_{12} was achieved in 97.7% (95% CI: 94.6% – 100.0%) of subjects. The LCB 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, SVR_{12} was achieved in 100.0% (95% CI: 95.9% – 100.0%) of subjects. The LCB 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 group was shown to be noninferior to the SVR_{12} rate for the 3-DAA + RBV group (treatment difference of 2.3% [95% CI: –0.8% – 5.4%], so the LCB was above the prespecified noninferiority margin of –10.5%).

Results for the additional efficacy endpoint of 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. The 2 subjects in the 3-DAA + RBV treatment group who did not achieve SVR_{12} and SVR_{24} prematurely discontinued study drug.

For treatment-experienced, HCV GT1b-infected adults without cirrhosis, 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 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 (42.0%) than in the 3-DAA treatment group (5.5%). The 3-DAA regimen was shown to be noninferior to the 3-DAA + RBV regimen for SVR_{12} rate. No virologic failure (on-treatment rebound or post-treatment relapse) was observed in either the 3-DAA + RBV or the 3-DAA treatment groups.

Summary/Conclusions (Continued)

Resistance Results:

Resistance analyses included 2 subjects in the nonPVF population who prematurely discontinued treatment. Subject [redacted] had no resistance-associated variants in NS3 or NS5B, but had R30Q in NS5A at baseline and R30Q + Y93H in NS5A at the time of treatment discontinuation. Absence of resistance-associated variants in NS3 and NS5B at the time of treatment discontinuation in Subject [redacted] was confirmed by clonal sequencing. Subject [redacted] had no resistance-associated variants in NS3 at baseline or at the time of treatment discontinuation, but Q54H was present in NS5A at baseline, and C316N + S556G were present in NS5B at baseline and at the time of treatment discontinuation. Absence of resistance-associated variants in NS3 and NS5A at the time of treatment discontinuation in Subject [redacted] was confirmed by clonal sequencing.

Patient-Reported Outcomes Results:

The majority of subjects in both treatment groups experienced decreases that did not meet criteria to be considered of minimal importance or increases 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 over baseline mean were observed after treatment for both treatment groups.

Pharmacokinetic Results:

Based on the binned C_{trough} values, the exposures achieved in pegIFN/RBV-experienced HCV GT1b-infected subjects in the present study for ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1 were comparable between Arm 1 and Arm 2 ($\leq$ 18% difference). RBV dosing does not appear to affect the concentrations of the DAAs or ritonavir.

Safety Results:

ABT-450/r/ABT-267 and ABT-333 coadministered with and without RBV for 12 weeks to pegIFN/RBV treatment-experienced, noncirrhotic, HCV GT1b-infected adults were generally well tolerated, with few subjects (2.2% 3-DAA + RBV, 0% 3-DAA) prematurely discontinuing study drug because of adverse events. While most subjects experienced at least 1 adverse event during the Treatment Period, most of these subjects experienced only mild adverse events.

The most common treatment-emergent adverse events were fatigue, headache, nausea, insomnia, pruritus, diarrhea, asthenia, and anemia in the 3-DAA + RBV treatment group and headache, fatigue, and diarrhea 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 regimen. Of the treatment-emergent adverse events reported for $\geq$ 5.0% of subjects in either treatment group, fatigue (31.9% versus 16.8%), nausea (20.9% versus 6.3%), insomnia (14.3% versus 3.2%), anemia (11.0% versus 0%), decreased appetite (9.9% versus 2.1%), blood bilirubin increased (8.8% versus 0%), and rash (8.8% versus 1.1%) 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 (8.8% versus 2.1%), rash-related events (24.2% versus 13.7%), and anemia-related adverse events (12.1% versus 0%), suggesting a causal or contributory role of RBV. These events were generally assessed as mild in severity.

Summary/Conclusions (Continued)

Safety Results (Continued):

No treatment-emergent deaths were reported. Four subjects (2 in each treatment group) experienced treatment-emergent serious adverse events during the Treatment Period. None of these events was considered by the investigator or AbbVie to be possibly or probably related to DAA treatment. No commonality was evident among the reported events.

Two subjects (both in the 3-DAA + RBV treatment group) experienced at least 1 adverse event that led to premature discontinuation of study drug during the Treatment Period. One of these events (pancreatitis) began prior to receiving study drug on Day 1. The event required hospitalization during the study and resulted in discontinuation of study drugs on Day 13. No specific adverse event led to premature discontinuation of study drug for more than 1 subject.

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 regimens were mainly mild and did not result in treatment interruption or discontinuation. There were no serious skin events.

Analysis of hematology parameters showed statistically significant differences between treatment groups in the mean change from baseline to the Final Treatment Visit in hemoglobin, hematocrit, red blood cell, reticulocyte count, platelet count, lymphocytes, monocytes, and activated partial thromboplastin time (APTT); however, no subjects had a PCS value in any of these laboratory parameters. The mean decrease in hemoglobin was 17.2 g/L greater in the 3-DAA + RBV group than in the 3-DAA group. Of note, mean change from baseline in hemoglobin for the 3-DAA group (mean hemoglobin of 147.1 g/L at baseline to 142.7 g/L at the Final Treatment Visit) suggested little or no impact on hemoglobin when RBV was not part of the DAA regimen. No subject in either treatment group experienced a grade 3 or greater hemoglobin value. There were no statistically significant differences between treatment groups in mean change from baseline to Final Post-Treatment Visit for any hematology parameter.

Analysis of chemistry parameters showed modest but statistically significant differences in mean change from baseline to Final Treatment Visit between treatment groups in uric acid, calcium, albumin, magnesium, glucose, cholesterol, insulin, triglycerides, and total protein. These changes were not considered to be clinically significant. The chemistry parameters with a statistically significant difference between treatment groups in mean change from baseline to the Final Post-Treatment Visit were glucose and albumin; however, the mean changes were small and not clinically meaningful. The percentages of subjects meeting prespecified criteria for PCS chemistry values were low for all parameters evaluated with the exception of total bilirubin.

For total bilirubin, a statistically significant difference in mean change from baseline to Final Treatment Visit was observed: +3.7 µmol/L for the 3-DAA + RBV treatment group compared with –1.0 µmol/L for the 3-DAA treatment group. In the 3-DAA + RBV treatment group, 8.8% of subjects had at least a grade 3 total bilirubin compared with no 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. Of the 8 subjects with a grade 3 bilirubin value, 3 had an associated symptomatic treatment-emergent adverse event of jaundice or ocular icterus; all 3 adverse events resolved.

Summary/Conclusions (Continued)

Safety Results (Continued):

Mean decreases were observed in alanine aminotransferase (ALT), AST, and gamma-glutamyl transferase (GGT) at the Final Treatment Visit, the Post-Treatment Week 4 Visit, and the Final Post-Treatment Visit, which were similar in both groups and consistent with clearance of HCV from the liver. No subject in either group experienced postbaseline elevations in ALT to > 5 × upper limit of normal (ULN). No cases were considered to be consistent with Hy's law.

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

Conclusions:

A 12-week regimen of ABT-450/r/ABT-267 and ABT-333 with or without RBV was generally well tolerated in pegIFN/RBV treatment-experienced, noncirrhotic, HCV GT1b-infected adults. A high SVR_{12} rate was achieved regardless of the inclusion of RBV. No subject in either treatment group experienced on-treatment virologic failure or post-treatment relapse. Both regimens were well tolerated, as evidenced by the low rate of treatment discontinuation and serious adverse events. The regimen without RBV was associated with fewer adverse events of fatigue, nausea, insomnia, decreased appetite, and rash, as well as a lower rate of laboratory abnormalities including bilirubin elevation and hemoglobin decrease. Overall, these results suggest that the 3-DAA regimen without RBV provides optimal safety and efficacy in this population.

Date of Report: 22Jul2015