2.0 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: <u>ABT-450:</u> (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate <u>ritonavir:</u> [5S-(5R*,8R*,10R*,11R*)]-10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester <u>ABT-267:</u> Dimethyl ([(2S,5S)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate <u>ABT-333:</u> (sodium N-{6-[3-*tert*-butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl]naphthalen-2-yl}methanesulfonamide) <u>Ribavirin:</u> 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide		

Title of Study: A Randomized, Open-Labeled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 and ABT-333 Co-administered with Ribavirin Compared to Telaprevir Co-administered with Pegylated Interferon α-2a and Ribavirin in Treatment-Experienced Adults with Chronic Hepatitis C Genotype 1 Virus Infection (MALACHITE-II)

Investigator: Ewa Janczewska, MD, PhD

Study Sites: 27 investigative sites in Argentina, Australia, Chile, Finland, Hungary, Poland, Romania, and Slovakia

Publications: 2

Studied Period (Years):	**Phase of Development:** 3b
First Subject First Visit: 18 June 2013 Last Subject Last Visit: 20 July 2015	

Objectives:

The primary objective of this study was to assess the efficacy (the percentage of subjects achieving 12-week sustained virologic response, SVR_{12}, [hepatitis C virus {HCV} RNA < lower limit of quantitation, LLOQ, 12 weeks post-treatment]) and safety of ABT-450/r/ABT-267 and ABT-333 coadministered with ribavirin (RBV) for 12 weeks compared to 12 weeks of treatment with telaprevir (TPV) and pegylated interferon (pegIFN)/RBV (TPV/PR) followed by either 12 weeks or 36 weeks of pegIFN/RBV, per local prescribing information, in treatment-experienced HCV genotype (GT) 1-infected adults.

The secondary objectives of this study were to compare the following health-related quality of life (HRQoL) and efficacy measures between the 2 treatment arms:

- the general HRQoL using the Short-Form 36 Health Survey (SF-36) Mental Component Summary scores;
- the general HRQoL using the SF-36 Physical Component Summary scores;
- the percentage of subjects with 24-week sustained virologic response rate (SVR_{24}) (the percentage of subjects with HCV RNA < LLOQ 24 weeks following treatment); and
- the percentage of subjects with virologic failure during treatment, and the percentage of subjects with post-treatment relapse.

Methodology:

This was a Phase 3b, randomized, open-label, parallel-arm, multicenter study in 2 parts, a Treatment Period and Post-Treatment Period. Approximately 150 HCV GT1-infected, pegIFN/RBV treatment-experienced, noncirrhotic adults were to be randomized to Arm A and Arm B in a 2:1 ratio:

- Arm A (3-direct-acting antiviral [DAA] + RBV): ABT-450/r/ABT-267 150 mg/100 mg/25 mg once daily (QD) and ABT-333 250 mg twice daily (BID) coadministered with RBV BID for 12 weeks;
- Arm B (TPV/PR): TPV 750 mg every 8 hours coadministered with pegIFN 180 µg subcutaneously (SC) weekly and RBV BID for 12 weeks followed by pegIFN 180 µg SC weekly and RBV BID for either 12 or 36 weeks, per local prescribing information.

Methodology (Continued):

Randomization was stratified by HCV subtype (1a versus non-1a) and type of response to previous pegIFN/RBV treatment (null responders versus partial responders versus relapsers). The duration of the study was planned to be up to 96 weeks (not including a Screening Period of up to 35 days). All subjects administered study drugs were followed for 48 weeks post-treatment to monitor safety, perform patient-reported outcome (PRO) assessments, and test for durability of antiviral response on HCV RNA (SVR) and emergence or persistence of resistance to DAAs.

The primary analysis occurred after all subjects completed through Post-Treatment Week 12 or prematurely discontinued the study.

Number of Subjects (Planned and Analyzed):

A total of 150 subjects were planned to be enrolled; 101 subjects in the 3-DAA + RBV arm and 47 subjects in the TPV/PR arm were enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV GT1-infected adults (18 to 65 years of age, inclusive) who were either null responders, partial responders, or relapsers to prior pegIFN/RBV treatment, with a body mass index ≥ 18 to < 38 kg/m^2. Females were either practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle), postmenopausal for at least 2 years, surgically sterile, or of childbearing potential and practicing 2 effective forms of birth control starting with Day 1 and for 7 months after stopping study drug (or as directed by the local RBV prescribing information) or sexually active with female partners only. Males must have been surgically sterile or agreed to practice 2 effective methods of birth control starting with Day 1 and for 7 months after stopping study drug (or as directed by the local RBV label) or sexually active with male partners only. Subjects had a chronic HCV 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	AbbVie[a]	Oral	Tablet	75 mg/50 mg/ 12.5 mg	12-006414 12-006474 12-008149
ABT-333	AbbVie[a]	Oral	Tablet	250 mg	12-003057 13-000242
Ribavirin	Roche	Oral	Tablet	200 mg	12-006116 12-006136

a. Abbott Laboratories at time of production.

Duration of Treatment:

Subjects in the 3-DAA + RBV arm were dosed for 12 weeks. Subjects in the TPV/PR arm received TPV with pegIFN and RBV for 12 weeks followed by pegIFN and RBV for either 12 weeks or 36 weeks, per local prescribing information. Response-guided therapy in the TPV/PR arm was only available for subjects who were relapsers to previous pegIFN/RBV therapy, as recommended per local prescribing information.

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

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
Ribavirin	Roche	Oral	Tablet	200 mg	12-006116 12-006136
Telaprevir	Janssen-Cilag	Oral	Film-coated Tablet	375 mg	12-008115 13-001428
Pegylated Interferon-α2a	Roche	SC injection	Syringe	180 µg/0.5 mL	12-005978 12-006673 12-007212 12-002372 12-003160

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:

There were no virologic failures among subjects receiving 3-DAA + RBV regimen. Therefore, no resistance testing was conducted. Resistance analyses of subjects in the TPV/PR arm failing treatment with TPV were conducted by Monogram Biosciences.

Patient-Reported Outcomes:

The impact on general HRQoL was assessed using the SF-36 version 2 (SF-36v2) non-disease specific HRQoL instrument. The change in disease-specific function and well-being was assessed using the HCV Patient Reported Outcomes (HCV-PRO) instrument. Health Utility was measured using the EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L) with visual analogue scale (VAS). Additional PRO assessments include the Work Productivity and Activity Impairment specific for HCV (WPAI-HCV) and the HCV Treatment Satisfaction Instrument (HCVTSat).

Pharmacokinetic:

Subjects randomized to the 3-DAA + RBV arm had individual plasma concentrations of ABT-267, ABT-333, ABT-333 M1, ABT-450, RBV, and ritonavir tabulated and summarized. Subjects randomized to the TPV/PR arm had plasma concentrations for TPV and RBV and serum concentrations for pegIFN determined at all study visits up to Week 12 only.

Safety:

The following safety evaluations were performed during the study: adverse event monitoring and vital signs, physical examination, electrocardiogram, and laboratory test 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 first 3 secondary endpoints in the order numbered below.

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

The simple percentage of subjects achieving SVR_{12} out of all intent-to-treat subjects was calculated and compared between Arm A and Arm B using a logistic regression model with treatment arm, baseline $\log_{10}$ HCV RNA level, HCV subtype (1a, non-1a), and previous type of response to pegIFN/RBV treatment (relapser, partial or null responder) as predictors at the $\alpha = 0.05$ significance level. If the logistic regression failed to converge, a stratum-adjusted Mantel-Haenszel approach was used, with HCV subtype (1a, non-1a) and previous type of response to pegIFN/RBV treatment (relapser, partial or null responder) as strata.

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

1. mean change from baseline to Final Treatment Visit in SF-36v2 Mental Component Summary score;
2. mean change from baseline to Final Treatment Visit in SF-36v2 Physical Component Summary score;
3. percentage of subjects with SVR_{24}.

Two additional secondary endpoints were summarized outside the sequential testing procedure:

- the percentage of subjects with virologic failure during treatment (defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment or confirmed HCV RNA ≥ LLOQ at the end of treatment); and
- the percentage of subjects with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ after the Final Treatment Visit through the SVR_{12} window among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment).

Patient-Reported Outcomes:

In addition to the assessment of prespecified PROs as key secondary endpoints, exploratory analyses of PROs were also performed, including but not limited to the following.

Summary statistics at each visit and for change from baseline to each visit by treatment arm were provided for the HCV-PRO total score, the EQ-5D-5L health index and VAS scores, and the SF-36v2 Physical Component Summary and Mental Component Summary scores. For each of these scores, mean change from baseline to Treatment Week 12, Final Treatment Visit, and Post-Treatment Week 12 was compared between treatment arms using an analysis of covariance model with treatment arm as a factor and baseline score and region as covariates.

For HCV-PRO total score and SF-36v2 Mental Component Summary and Physical Component Summary measures, continuous plots by treatment arm were 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 show change from baseline to Final Treatment Visit and change from baseline to Treatment Week 12.

Statistical Methods (Continued):

Patient-Reported Outcomes (Continued):

The minimally important difference (MID) during treatment for the SF-36v2 was defined as a decrease of 5 points from baseline for both the Physical Component Summary and Mental Component Summary scores. The MID during treatment was calculated for the HCV-PRO total score and the EQ-5D-5L health index using receiver operating characteristic curves with a change from baseline to Final Treatment Visit of –5 points in the SF-36v2 Physical Component Summary and Mental Component Summary measures as anchors. The calculated MIDs using SF-36v2 Physical Component Summary and Mental Component Summary as anchors were averaged. The percentage of subjects with a change from baseline to Final Treatment Visit in each of these measures > the appropriate MID was compared between treatment arms using Fisher's exact tests.

The responses to HCVTSat, which were collected upon treatment completion or discontinuation, were summarized by 2 scores: 1) a global measure of treatment satisfaction (final item scored 1 to 10) and 2) a composite index measure (average of 9 items scored 1 to 5). Summary statistics for each treatment arm were provided for the 2 summary scores. Pairwise comparisons of the 2 summary scores between the treatment arms were performed using analysis of variance (ANOVA) with treatment arm as the factor.

Pharmacokinetics:

Plasma concentrations of ABT-450, ABT-267, ABT-333, ABT-333 M1 metabolite, ritonavir, and RBV were tabulated for each subject in the 3-DAA + RBV arm. Plasma concentrations of TPV and RBV and serum concentrations of pegIFN were tabulated for each subject in the TPV/PR arm up to Week 12. Summary statistics were computed based on time after dose and/or visit.

Safety:

All subjects who received at least 1 dose of study drug were included in the safety analyses. The number and percentage of subjects in each treatment arm with treatment-emergent adverse events (i.e., any event that began or worsened in severity after initiation of study drug through 30 days post-study drug dosing) were tabulated by primary Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and preferred term and compared between treatment arms using Fisher's exact tests. The tabulation of the number of subjects with treatment-emergent adverse events by severity rating and relationship to each study drug (AbbVie DAAs, RBV, TPV, or pegIFN) was also provided. To account for different treatment durations, exposure-adjusted adverse event analyses and a Week 12 truncated adverse event analysis were conducted for each treatment arm.

Change from baseline in laboratory tests and vital sign measurements to each time point of collection during the Treatment Period, including Final Treatment Visit, was summarized by treatment group and compared between arms using an ANOVA model with treatment group as the 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 test.

Summary/Conclusions

Efficacy Results:

The primary efficacy endpoint was the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). SVR_{12} was achieved by 101/101 (100.0%) subjects in the 3-DAA + RBV arm and by 31/47 (66.0%) subjects in the TPV/PR arm. The stratum-adjusted difference between the SVR_{12} rates for the 3-DAA + RBV and TPV/PR arms was 34.26% (95% CI: 21.1 to 47.4) with $P < 0.001$. The proportion of subjects achieving SVR_{12} in the 3-DAA + RBV arm was greater than in the TPV/PR arm in all subgroups evaluated.

In the 3-DAA + RBV arm, there were no virologic failures (on-treatment virologic failure or post-treatment relapse). In the TPV/PR arm, 9/47 (19.1%) subjects experienced on-treatment virologic failure and 2/32 (6.3%) subjects experienced post-treatment relapse for a total of 23.4% (11/47) virologic failures.

Sensitivity analyses that evaluated alternative methods to impute missing post-treatment virologic results were consistent with the primary analysis. A test of heterogeneity was conducted within each treatment arm and indicated no significant heterogeneity ($P = 0.289$) across the randomization strata defined by HCV subgenotype (GT1a, GT1b) and previous response to pegIFN/RBV treatment (pegIFN/RBV null responder, pegIFN/RBV partial responder, pegIFN/RBV relapser). The 95% CI based on the stratum-adjusted variance was 100.0% to 100.0% for the 3-DAA + RBV arm and 52.6% to 79.3% for the TPV/PR arm.

Among the secondary endpoints, statistically significant differences were observed between the 3-DAA + RBV and TPV/PR arms for mean change in SF-36v2 Mental and Physical Component Summary scores from baseline to Final Treatment Visit. These results indicated that the 3-DAA + RBV regimen had significantly less unfavorable impact on HRQoL, as measured by SF-36v2 Mental Component Summary and Physical Component Summary compared to the TPV/PR arm. Additionally, subjects in the 3-DAA + RBV arm achieved a statistically significantly higher SVR_{24} rate than subjects in the TPV/PR arm (99.0% versus 66.0%).

Patient-Reported Outcomes Results:

Compared with the TPV/PR regimen, the 3-DAA + RBV regimen had significantly less unfavorable impact on subject's HRQoL, function, and wellbeing (per SF-36v2 Physical Component Summary score, SF-36v2 Mental Component Summary score, and HCV-PRO total score) during or at the end of treatment. Furthermore, the 3-DAA + RBV regimen had only minimal impact on work productivity and daily activity; in contrast, the TPV/PR regimen was associated with notable impairments in work productivity and daily activity during or at the end of treatment. Satisfaction with treatment with the 3-DAA + RBV regimen was statistically significantly greater compared with the TPV/PR regimen. In general, sustained improvements in subjects' HRQoL, function, and well-being were observed at the Final Post-Treatment Visit for all regimens.

Summary/Conclusions (Continued)

Pharmacokinetic Results:

Based on the binned C_{trough} values in the 3-DAA + RBV arm, the exposures achieved in HCV treatment-experienced subjects in the present study for ABT-450, ABT-267, ABT-333, and ABT-333 M1 were within the range of exposures achieved in previous Phase 3 studies conducted in treatment-naïve or treatment-experienced HCV GT1-infected adults. The geometric mean of ritonavir binned C_{trough} values was 9% to 56% higher than previous Phase 3 studies. The arithmetic mean of the binned C_{trough} values of RBV was within the range of previously reported values.

In the TPV/PR arm, the binned C_{trough} arithmetic mean value for TPV was approximately 65% higher in the present study than reported values. The arithmetic mean of the binned C_{trough} values of RBV was within the range of values previously reported. The arithmetic mean of the serum concentrations of pegIFN (Week 12) reported in the present study was comparable (< 13% difference) to reported values.

Safety Results:

The safety population included all randomized subjects who received at least 1 dose of study drug (N = 148).

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks in treatment-experienced HCV GT1-infected adults without cirrhosis was well tolerated, as demonstrated by the low rate of treatment-emergent serious adverse events; in addition, no subject prematurely discontinued study drug due to a treatment-emergent adverse event. The TPV/PR regimen was not as well tolerated, with a greater frequency and severity of adverse events, and with 10.6% of subjects discontinuing treatment due to adverse events.

While most subjects experienced at least 1 adverse event during the Treatment Period, most of these adverse events were mild in the 3-DAA + RBV arm. In contrast, most subjects in the TPV/PR arm experienced an event that was at least moderate in severity.

The most common treatment-emergent adverse events in the 3-DAA + RBV arm were headache, pruritus, and fatigue. These adverse events were comparable in nature and frequency to those reported in other studies using the 3-DAA + RBV regimen. The most common treatment-emergent adverse events in the TPV/PR arm were headache, nausea, pruritus, asthenia, anemia, pyrexia, neutropenia, fatigue, cough, anal pruritus, rash, insomnia, myalgia, decreased appetite, arthralgia, dizziness, dry skin, vomiting, alopecia, nasopharyngitis, chills, leukopenia, abdominal pain, and irritability. These events are consistent with the reported safety profiles of TPV, RBV, and/or pegIFN. Of these events, anemia, leukopenia, neutropenia, anal pruritus, nausea, vomiting, asthenia, pyrexia, decreased appetite, arthralgia, myalgia, insomnia, irritability, cough, alopecia, dry skin, pruritus, and rash occurred statistically significantly more frequently ($P \leq 0.05$) in the TPV/PR treatment arm than in the 3-DAA + RBV treatment arm. These events are known to be associated with TPV/PR treatment.

One nontreatment-emergent death was reported. A 3-DAA + RBV subject died due to a serious adverse event of diffuse large B-cell lymphoma that began 206 days after the last dose of study drug and was considered by the investigator to have no reasonable possibility of relationship to any study drug.

Six subjects (one 3-DAA + RBV, 5 TPV/PR) experienced treatment-emergent serious adverse events. Two TPV/PR subjects experienced an event of anemia assessed by the investigator to have a reasonable possibility of relationship to RBV and an event of eczema was considered by the investigator to have a reasonable possibility of relationship to TPV. The treatment-emergent serious adverse events in the 3-DAA + RBV arm (appendicitis and epilepsy in 1 subject) were considered by the investigator to have no reasonable possibility of relationship to any study drug.

Summary/Conclusions (Continued)

Safety Results (Continued):

Among the adverse events of interest, a similar proportion of subjects experienced bilirubin-related adverse events in the 3-DAA + RBV and TPV/PR treatment arms (5.0% and 4.3%, respectively). The results in the 3-DAA + RBV arm are consistent with those of other Phase 3 clinical studies of 3-DAA + RBV. Transient elevations in bilirubin are expected effects of ABT-450 and TPV, known inhibitors of the organic anion transporting polypeptide 1B1 bilirubin transporter; elevations have also been observed in subjects treated with pegIFN. In addition, RBV-associated hemolysis can also result in hyperbilirubinemia.

A greater percentage of subjects in the TPV/PR arm than in the 3-DAA + RBV arm experienced rash-related adverse events (55.3% versus 14.9%), anemia-related adverse events (34.0% versus 3.0%), and treatment-emergent adverse events of special interest for neutropenia (27.7% versus 1.0%), thrombocytopenia (8.5% versus 0%), and psychiatric disorders (21.3% versus 9.9%) based on standardized MedDRA query/company MedDRA query search criteria. These events were generally assessed as mild or moderate in severity. Anemia and rash are well-known side effects of TPV and RBV treatment, and neutropenia, thrombocytopenia, and serious neuropsychiatric disorders are risks of pegIFN treatment.

Review of the specific MedDRA search queries for rash revealed that events of rash and pruritus were statistically significantly more frequent in the TPV/PR arm than in the 3-DAA + RBV arm. The events reported in each arm were mainly mild and did not result in treatment interruption or discontinuation. There was 1 treatment-emergent serious rash event (eczema in a TPV/PR subject).

Analysis of hematology parameters showed statistically significant differences between arms for mean change from baseline to the Final Treatment Visit in hemoglobin, hematocrit, red blood cell count, reticulocytes, platelet count, white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils. The mean changes in monocytes, eosinophils, and basophils were small in each treatment arm. In the TPV/PR arm, the mean decreases from baseline in platelet count, WBC count, total neutrophils, and lymphocytes were consistent with the known effects of pegIFN. There was a greater mean increase from baseline in reticulocyte count in the 3-DAA + RBV treatment arm than in the TPV/PR treatment arm. This difference is due to the fact that 3-DAA regimen allows for reticulocytosis, as a compensatory mechanism, to occur in response to the anemia resulting from RBV, while pegIFN in the TPV/PR regimen suppresses the compensatory reticulocytosis in response to RBV-associated anemia.

The mean decrease in hemoglobin was 5.8 g/L greater ($P \leq 0.05$) in the TPV/PR treatment arm than in the 3-DAA + RBV treatment arm at the Final Treatment Visit, suggesting a greater impact of TPV and pegIFN on hemoglobin than DAA therapy. No subject in the 3-DAA + RBV treatment arm and 4 (8.5%) subjects in the TPV/PR treatment arm experienced a reduction from baseline to a grade 3 hemoglobin value.

No more than 1 subject in the 3-DAA + RBV treatment arm experienced a PCS value for any hematology parameter. Approximately half of the subjects (51.1%) in the TPV/PR treatment arm had PCS low total neutrophil values; 40.4% of subjects had PCS low WBC count, and 14.9% of subjects had PCS low lymphocyte count.

Analysis of chemistry parameters showed small but statistically significant differences in mean change from baseline to Final Treatment Visit between treatment arms in inorganic phosphate, magnesium, sodium, bicarbonate, and triglycerides that were not considered clinically significant. For total bilirubin, similar mean changes from baseline were observed at most time points during treatment.

Summary/Conclusions (Continued)

Safety Results (Continued):

PCS values for chemistry parameters were infrequent, occurring in no more than 1 subject in the 3-DAA + RBV arm or 3 subjects in the TPV/PR arm, with the exception of total bilirubin in both treatment arms and triglycerides in the TPV/PR arm. One subject in each treatment arm had at least a grade 3 postbaseline total bilirubin. This suggests that the effect of the 3-DAA + RBV regimen and the TPV/PR regimen on total bilirubin is similar.

Mean decreases from baseline were observed in alanine aminotransferase (ALT) and AST at the Final Treatment Visit, Post-Treatment Week 4 Visit, and Final Post-Treatment Visit, which were similar in both treatment arms. One (1.0%) subject in the 3 DAA + RBV treatment arm and 3 (6.4%) subjects in the TPV/PR treatment arm experienced postbaseline elevations in ALT to > 5 × upper limit of normal, which improved without study drug interruption or discontinuation in the 3 DAA + RBV subject. One 3 DAA + RBV subject and 3 TPV/PR subjects had ALT and total bilirubin values that met biochemical criteria for inclusion in Hy's law quadrant of an evaluation of drug-induced serious hepatotoxicity plot, but none of these were considered Hy's law cases.

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

In summary, adverse event and laboratory safety data in this study demonstrate that the 3-DAA + RBV regimen is better tolerated than the TPV/PR regimen in treatment-experienced, HCV GT1-infected subjects. Key differences in the safety profiles of these 2 regimens include a greater frequency of adverse events, drug-related adverse events, serious adverse events, and adverse events leading to premature treatment discontinuation in the TPV/PR arm than in the 3-DAA with RBV arm. In addition, a higher frequency of rash-related adverse events, anemia-related adverse events, psychiatric disorder-related adverse events, and adverse events of neutropenia and thrombocytopenia occurred with the TPV/PR regimen compared with the 3-DAA + RBV regimen.

Conclusions:

Treatment-experienced, HCV GT1-infected adults without cirrhosis who were treated with a 12-week regimen of ABT-450/r/ABT-267 and ABT-333 with RBV achieved a statistically significantly higher SVR_{12} rate than subjects treated for 24 to 48 weeks with the TPV/PR regimen (100.0% versus 66.0%). These results are consistent with previous reports on the 3-DAA and TPV/PR regimens.

Compared with the TPV/PR regimen, the 3-DAA + RBV regimen had significantly less unfavorable impact on subject's HRQoL, function, and wellbeing (per SF-36v2 Physical Component Summary score, SF-36v2 Mental Component Summary score, and HCV-PRO total score) during or at the end of treatment. Furthermore, the 3-DAA + RBV regimen had only minimal impact on work productivity and daily activity; in contrast, the TPV/PR regimen was associated with notable impairments in work productivity and daily activity during or at the end of treatment. Satisfaction with treatment with the 3-DAA + RBV regimen was statistically significantly greater compared with the TPV/PR regimen. In general, sustained improvements in subjects' HRQoL, function, and well-being were observed at the Final Post-Treatment Visit for all regimens.

Summary/Conclusions (Continued)

Conclusions (Continued):

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 safety profile observed in the 3-DAA + RBV arm was consistent with that observed for the combination of 3 DAAs with RBV in previous studies. Consistent with the reported safety profile of TPV/PR in the TPV Summary of Product Characteristics, the TPV/PR regimen was not as well tolerated, with 10.6% of subjects discontinuing study treatment due to adverse events. In addition, the lower tolerability of TPV/PR treatment likely reduced treatment success for the regimen, since 4 of the 5 subjects who prematurely discontinued TPV/PR treatment due to adverse events failed to achieve SVR_{12}. The RBV-associated toxicities, such as anemia, occurred at much higher frequency and with greater severity in combination with pegIFN than in combination with 3-DAA treatment.