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, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-II)		
Investigator: Fred Poordad, MD		
Study Sites: 78 investigative sites in the United States, Puerto Rico, Canada, Belgium, France, Germany, Italy, Spain, and the United Kingdom		
Publications: 10		

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 24 October 2012 Last Subject Last Visit: 24 September 2014	

Objectives:

The primary objectives of this study were to assess the safety and to compare the sustained virologic response 12 weeks postdosing (SVR_{12}) rates (the percentage of subjects achieving a 12-week sustained virologic response, SVR_{12} [HCV ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks following treatment]) of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 or 24 weeks to the historical SVR rate of telaprevir plus pegylated interferon (pegIFN) and RBV in HCV genotype 1-infected adults with compensated cirrhosis.

The secondary objectives of this study were to compare the SVR_{12} rates between the 12- and 24-week treatment arms and assess the percentage of subjects with virologic failure during treatment and the percentage of subjects with relapse post-treatment.

Methodology:

This was a Phase 3, randomized, open-label, multicenter study evaluating the safety and efficacy of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 or 24 weeks in HCV genotype 1, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis. Subjects meeting the eligibility criteria were randomized to the 12- and 24-week treatment arms until approximately 380 subjects were enrolled at approximately 75 sites. The treatment arms were:

- Arm A: ABT-450/r/ABT-267 150 mg/100 mg/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) + RBV for 12 weeks;
- Arm B: ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID + RBV for 24 weeks

RBV dosing was weight based, either 1,000 mg or 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).

Subjects were stratified by receipt of previous pegIFN/RBV treatment (treatment-experienced) versus treatment-naïve. The treatment-naïve subjects were further stratified by HCV subgenotype (1a versus non-1a) and by interleukin 28B (IL28B) genotype (CC versus non-CC). The treatment-experienced subjects were further stratified by type of nonresponse to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) and by HCV subgenotype (1a versus non-1a).

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

- Null responder:
  - 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 (Weeks 10 – 16); or
  - received at least 4 weeks of pegIFN/RBV for the treatment of HCV and achieved a < 1 $\log_{10}$ IU/mL reduction in HCV RNA at Week 4 (≥ 25 days);
- Partial responder: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved ≥ 2 $\log_{10}$ IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment;

Methodology (Continued):

- Relapser: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at or after the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up.

During the Treatment Period, subjects received treatment with ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for either 12 or 24 weeks. Upon completing the Treatment Period or premature discontinuation of the Treatment Period, subjects entered the 48-week Post-Treatment Period.

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

Safety and efficacy evaluations occurred throughout the study. Virologic stopping criteria were evaluated for individual subjects. Efficacy evaluations were conducted to evaluate if add-on pegIFN treatment was needed based on rates of breakthrough and if the duration of treatment needed to be extended based on rates of relapse. Interim summaries of safety and virologic data were provided to an independent Data Monitoring Committee for further review throughout the study. These treatment adjustment criteria were not met.

Number of Subjects (Planned and Analyzed):

Approximately 380 subjects were planned to be enrolled; 380 subjects (208 Arm A, 172 in Arm B) were enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV genotype 1-infected, treatment-experienced or treatment-naïve adults (18 to 70 years of age, inclusive) with cirrhosis, and with a body mass index ≥ 18 to < 38 kg/m^2. Females were either practicing total abstinence from sexual intercourse, sexually active with female partners only, 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, had male partners only, or agreed to practice 2 effective methods of birth control throughout the course of the study. Subjects had a chronic HCV genotype 1 infection, a plasma HCV RNA > 10,000 IU/mL, and documentation of cirrhosis (e.g., a Metavir score > 3 or an Ishak score > 4) or FibroScan® result ≥ 14.6 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 mg/ 50 mg/ 12.5 mg	12-005575 12-006474
ABT-333	Abbott/AbbVie	Oral	Tablet	250 mg	12-003057 12-002614
Ribavirin	Roche or Kadmon Pharmaceuticals, LLC[a]	Oral	Tablet	200 mg	12-006117 12-002459

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 lot 12-002459 were manufactured by Kadmon Pharmaceuticals, LLC and lot 12-006117 was manufactured by Roche.

Duration of Treatment: Subjects received ABT-450/r/ABT-267 and ABT-333 with RBV for 12 or 24 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 assessed at all Treatment Period visits and at all post-treatment visits.

Resistance:

For subjects who 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 (HCV-PRO) instrument. Health State Utility was measured using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L) instrument. General Health Related Quality of Life (HRQoL) was assessed using the Short Form 36, version 2 (SF-36v2) non-disease specific HRQoL instrument.

Pharmacokinetic:

Plasma concentrations for ABT-450, ritonavir, ABT-333, ABT-333 M1 metabolite, ABT-267, and RBV were determined in samples harvested at each study visit; 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, and vital signs.

Statistical Methods

Efficacy:

Multiplicity was controlled across the primary efficacy comparisons with a gatekeeping approach and splitting the overall 2-sided significance level of 0.05 between the 2 arms using a Bonferroni correction of 0.025 for each arm. The primary endpoints within Arm A were tested separately from Arm B in the following order:

A1. Noninferiority of Arm A (12-week treatment) to the historical SVR rate for telaprevir plus pegIFN and RBV therapy;

A2. Superiority of Arm A to the historical SVR rate for telaprevir plus pegIFN and RBV therapy;

B1. Noninferiority of Arm B (24-week treatment) to the historical SVR rate for telaprevir plus pegIFN and RBV therapy;

B2. Superiority of Arm B to the historical SVR rate for telaprevir plus pegIFN and RBV therapy.

Statistical Methods (Continued)

Efficacy (Continued):

Within Arm A, only if success was demonstrated for noninferiority of the SVR_{12} rate in Arm A to the historical rate for telaprevir plus pegIFN and RBV therapy (A1) did the testing continue to superiority of the SVR_{12} rate in Arm A to the historical rate for telaprevir plus pegIFN and RBV therapy (A2). Within Arm B, only if success was demonstrated for noninferiority of the SVR_{12} rate in Arm B to the historical rate for telaprevir plus pegIFN and RBV therapy (B1) did testing continue to superiority of the SVR_{12} rate in Arm B to the historical rate for telaprevir plus pegIFN and RBV therapy (B2). Otherwise, statistical testing stopped. If success was achieved for all of the primary endpoints (A1, A2, B1, and B2), the first secondary endpoint to compare the percentage of subjects with SVR_{12} following 12 or 24 weeks of treatment was tested; otherwise, statistical testing stopped.

The percentage and a 2-sided 97.5% confidence interval (CI) of subjects achieving SVR_{12} within each arm were calculated using the simple proportion and variance, and the normal approximation to the binomial distribution was used to estimate the CI. To test the hypothesis that the percentage of treatment-naïve and pegIFN/RBV treatment-experienced HCV genotype 1-infected subjects with compensated cirrhosis treated with ABT-450/r/ABT-267 + ABT-333 + RBV for 12 or 24 weeks who achieve SVR_{12} is noninferior or superior to the historical SVR rate for the corresponding population treated with telaprevir plus pegIFN and RBV, the lower confidence bound (LCB) of the 97.5% CI must be greater than 43% in order for the regimen to be considered noninferior, and the LCB of the 97.5% CI of the SVR_{12} rate must be greater than 54% in order for the regimen to be considered superior. The value of 54% used in the endpoints as the historical SVR rate for telaprevir plus pegIFN and RBV represents the upper confidence bound of the 2-sided 95% CI of the combined telaprevir-based SVR rate. The value of 43% used for the noninferiority comparison represents the historical SVR rate (54%) adjusted for a noninferiority margin of 10.5%.

The secondary efficacy endpoint included in the gatekeeping testing procedure was the percentage of subjects with SVR_{12} in Arm B compared with Arm A. Other secondary endpoints not included in the gatekeeping testing procedure were:

- the percentage of subjects in each arm with on-treatment virologic failure during the Treatment Period (defined as confirmed HCV RNA $\geq$ LLOQ after HCV RNA < LLOQ during treatment, 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 failure to suppress [never achieving HCV RNA < LLOQ] during treatment of at least 6 weeks [$\geq$ 36 days]);
- the percentage of subjects in each arm with post-treatment relapse (defined as confirmed HCV RNA $\geq$ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment).

To test the hypothesis that the percentages of subjects who achieve SVR_{12} is different between Arm A and Arm B, the percentages were compared using a logistic regression model with treatment arm, baseline $\log_{10}$ HCV RNA level, HCV subgenotype (1a, non-1a), IL28B genotype (CC, non CC), and pegIFN/RBV treatment history (treatment-naïve or treatment-experienced) as predictors.

The percentages (with 2-sided 95% CIs using the normal approximation to the binomial distribution) of the subjects with on-treatment virologic failure and post-treatment relapse were calculated with simple proportion and variance and summarized for each arm. These endpoints were not part of the multiple testing procedure, as no hypothesis was being tested.

Statistical Methods (Continued)

Resistance:

The following resistance information was analyzed for subjects who received active drugs and 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 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-36 Mental Component Summary and SF-36 Physical Component Summary decrease of 5 points.

Pharmacokinetics:

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. Summary statistics were computed for each time and visit.

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 percentages of subjects with PCS values during the Treatment Period were compared between arms using Fisher's exact tests.

Summary/Conclusions

Efficacy Results:

Sustained virologic response 12 weeks postdosing was achieved by 191/208 (91.8%) subjects in Arm A (97.5% CI: 87.6% – 96.1%) and by 166/172 (96.5%) subjects in Arm B (97.5% CI: 93.4% – 99.7%). For Arm A and Arm B, the LCB was above 43% (noninferiority threshold) and 54% (superiority threshold). Therefore, both 12-week and 24-week treatment with 3-direct-acting antiviral agent (DAA) + RBV demonstrated noninferiority and superiority to the historical control rate for telaprevir plus pegIFN and RBV therapy. Sensitivity analyses that evaluated alternative methods to impute missing post-treatment virologic results were consistent with the primary analysis.

In Arm A, 1 (0.5%) subject experienced on-treatment virologic rebound and 12 (5.9%) subjects experienced relapse through Post-Treatment Week 12 for a total of 6.3% (13/208) virologic failures. In Arm B, 3 (1.7%) subjects experienced on-treatment virologic rebound and 1 (0.6%) subject experienced relapse through Post-Treatment Week 12 for a total of 2.3% (4/172) virologic failures.

The percentage of subjects with SVR_{12} in Arm A compared with Arm B was the only secondary endpoint for which formal hypothesis testing was performed. The adjusted difference between arms was not statistically significant.

For HCV genotype 1-infected adults with cirrhosis, noninferiority and superiority were demonstrated for both 12-week and 24-week treatment with 3 DAAs + RBV for SVR_{12} relative to the historical control rate for telaprevir plus pegIFN and RBV therapy. The observed rate of virologic failures (on-treatment rebound or post-treatment relapse) was 6.3% and 2.3% in Arm A and Arm B, respectively.

In a stepwise logistic regression model fitted to subjects in the intent-to-treat population, the subgroup variables of HCV prior experience (null responders had lower odds of SVR_{12} than non-null responders), HCV genotype (1a had lower odds of SVR_{12} than non-1a), and former injection drug use (users had lower odds of SVR_{12} than non-users) were identified as having a statistically significant association with SVR_{12}.

The SVR_{12} rates observed in this study are generally similar to those observed with this regimen in noncirrhotic subjects. For most subgroups, a longer duration of therapy did not result in significantly higher SVR rates. Among genotype 1a prior null responders, a numerically higher SVR_{12} rate was observed in Arm B versus Arm A (92.9% versus 80.0%) suggesting that, for this subgroup, a treatment duration of 24 weeks is preferable. Among genotype 1a treatment-naïve and genotype 1a treatment-experienced subjects without prior null response to pegIFN/RBV, a 12-week treatment duration is sufficient.

An overall SVR_{12} rate of 95.0% (190/200) is estimated for the compensated cirrhotic population with a dosing recommendation for 24 weeks for HCV genotype 1a prior null responders and 12 weeks for other patients, by pooling the SVR_{12} rate for HCV genotype 1a prior null responders from Arm B (39/42, 92.9%) with the SVR_{12} rate from Arm A excluding HCV genotype 1a prior null responders (151/158, 95.6%).

Summary/Conclusions (Continued)

Efficacy Results (Continued):

The presence of a serum alpha fetoprotein ≥ 20 ng/mL, platelet count < 90×10^9/L, or serum albumin < 35 g/L at baseline was significantly associated with a higher likelihood of relapse among HCV genotype 1a-infected subjects in Arm A. This suggests that a treatment duration of 24 weeks may be preferable to minimize the risk of relapse for HCV genotype 1a patients with the baseline presence of any of these laboratory markers of more advanced cirrhosis. Among genotype 1a-infected subjects with a baseline serum alpha fetoprotein < 20 ng/mL, platelet count ≥ 90×10^9/L, and serum albumin ≥ 35 g/L, a 12-week treatment duration is sufficient.

Results for the additional efficacy endpoint of sustained virologic response 24 weeks postdosing were consistent with the primary efficacy results with 99.0% and 99.4% agreement between SVR_{12} and SVR_{24} for Arm A and Arm B, respectively.

In Arm A, relapses were observed in 13 (6.4%) subjects; 12 subjects by Post-Treatment Week 12 and 1 subject during the SVR_{24} window. In Arm B, relapses were observed in 2 (1.2%) subjects; 1 subject by Post-Treatment Week 12 and 1 subject who relapsed after achieving SVR_{24}.

Overall, virologic failure (on-treatment rebound or post-treatment relapse) was observed in 14/208 (6.7%) subjects in Arm A and 5/172 (2.9%) subjects in Arm B.

Resistance Results:

Resistance analyses of the PVF population included 19 subjects, of whom 18 were genotype 1a-infected and 1 was genotype 1b-infected; 14 subjects were in the 12-week arm and 5 subjects were in the 24-week arm. Q80K in NS3 was detected at baseline in the 12-week arm at a higher proportion in the PVF population compared with the matched set of subjects who achieved SVR_{12}. This difference may be due, in part, to relatively low baseline Q80K prevalence in the selected matched control comparison group (15.4%). In addition, in a subsequent analysis of subjects limited to those receiving the recommended regimen (i.e., genotype 1a-infected prior null responder subjects receiving 24 weeks of treatment and genotype 1a-infected prior non-null responder subjects receiving 12 weeks of treatment), there was no association between outcome and prevalence of Q80K in the PVF population. There was no association between treatment outcome and Q80K prevalence in the 24-week arm, nor with any other baseline variants at signature resistance-associated amino acid positions. The predominant variants in the genotype 1a-infected subjects in the PVF population at the time of failure were D168V in NS3; M28T and Q30R in NS5A; and A553T/V, and S556G in NS5B. Of the 18 genotype 1a-infected subjects in the PVF population, 16 had resistance-associated variants in at least 1 target and 11 had resistance-associated variants in all 3 targets at the time of failure. The single genotype 1b-infected subject in the PVF population had Y93H in NS5A at baseline and at the time of failure, and also had variants D168V in NS3, and C316Y and M414I in NS5B at the time of failure. The 3 genotype 1a-infected subjects in the non-PVF population who prematurely discontinued treatment and had sequencing data available had Q80K in NS3 at baseline but did not have resistance-associated variants in NS3 or NS5B at the time of treatment discontinuation. Two of the subjects had Q30R and/or M28V in NS5A at the time of treatment discontinuation, and 1 subject had M28V in NS5A at baseline and 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 13, 15, and 13 of the 18 genotype 1a-infected subjects in the PVF population, respectively. Variants in NS3 declined through Post-Treatment Week 24 (8/11, 73%) and Post-Treatment Week 48 (1/8, 13%). Treatment-emergent resistance-associated variants in NS5A and NS5B remained detectable at similar levels through Post-Treatment Week 48.

Patient-Reported Outcomes Results:

The majority of subjects in both arms experienced decreases (that did not meet criteria to be considered even of minimal importance) or increases from the 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.

Pharmacokinetic Results:

The plasma concentrations at 2 hours post-study drug dosing on Day 1 for ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and RBV were comparable (< 22% difference) between Arm A and Arm B. Based on the C_{trough} values, the exposures achieved in the present study for ABT-450, ABT-267, ritonavir, ABT-333, ABT-333 M1, and RBV in pegIFN/RBV treatment-naïve and treatment-experienced HCV genotype 1-infected adults with compensated cirrhosis are comparable (≤ 25% difference) between both treatment arms (12-week and 24-week duration).

The C_{trough} plasma concentrations of ABT-450 from this study were approximately 3.16- to 3.41-fold higher, and the C_{trough} plasma concentrations of ABT-267, ritonavir, ABT-333, ABT-333 M1, and RBV were 0.86- to 1.56-fold when compared with concentrations from the interim results of Studies M11-646, M13-098, and M13-961.

Safety Results:

ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 or 24 weeks to HCV genotype 1, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis was generally well tolerated, with few subjects (1.9% Arm A [12-week], 2.3% Arm B [24-week]) prematurely discontinuing study drug because of 1 or more treatment-emergent adverse events. The majority of subjects (91.8% Arm A, 91.3% Arm B) experienced 1 or more treatment-emergent adverse event during the Treatment Period. Most of these subjects experienced events that were mild or moderate in severity.

Treatment-emergent adverse events reported for ≥ 10.0% of subjects were fatigue, headache, pruritus, nausea, insomnia, diarrhea, asthenia, cough, and rash in both treatment arms, and irritability, dyspnea, and anemia in Arm B.

Adverse events of fatigue, upper respiratory tract infection, back pain, memory impairment and dyspnea occurred at a statistically significant higher rate in Arm B. However, the majority of these adverse events occurred during the first 84 days in Arm B and, therefore, may not be attributable to the longer period of exposure. Only back pain occurred more frequently after the first 84 days of treatment than during the first 84 days of treatment.

Summary/Conclusions (Continued)

Safety Results (Continued):

The overall incidence of treatment-emergent serious adverse events (5.3%) and treatment-emergent adverse events leading to premature discontinuation of study drug (2.1%) was low, with no statistically significant difference noted between arms. No commonality was evident among these events.

No treatment-emergent deaths were reported; there were 3 nontreatment-emergent deaths, none of which were considered associated with DAA or RBV treatment by the investigator. One subject in Arm A died due to nontreatment-emergent adverse events of multi-organ failure and septic shock that began 80 days after the last dose of study drug. These events were considered by the investigator to have no reasonable possibility of relationship to DAA or RBV treatment. Another subject in Arm A died due to hepatocellular carcinoma, which was diagnosed on Day 171 (Post-Treatment Day 86), and renal failure. The investigator considered these events to have no reasonable possibility of relationship to either DAA or RBV. The third subject, also in Arm A, experienced an event of esophageal varices haemorrhage diagnosed on Day 362 (Post-Treatment Day 277) and died due to decompensation after variceal bleed and multisystem organ failure. The investigator considered the event to have no reasonable possibility of being related to DAA or RBV.

Analyses of rash-related events, liver function test values, and hepatic-related events during this study showed no new or different pattern compared with other clinical studies of AbbVie DAAs with RBV in subjects without cirrhosis. However, a greater frequency of anemia-related events was observed in this study compared with clinical studies of AbbVie DAAs with RBV in subjects without cirrhosis, suggesting that underlying cirrhosis may increase the risk of these events.

The rates and magnitude of bilirubin elevation were higher in this cirrhotic population compared with the noncirrhotic population evaluated in other studies. Although these elevations were predominantly indirect bilirubin, some subjects had parallel increases in direct bilirubin, possibly due to decreased elimination of conjugated bilirubin associated with underlying cirrhosis. Similar to the noncirrhotic subjects, the bilirubin in general peaked at Week 1 and declined towards baseline by the end of treatment. Symptomatic hyperbilirubinemia was infrequent and no subject discontinued due to symptomatic hyperbilirubinemia. Some subjects experienced elevations in bilirubin in the presence or absence of ALT elevations. In all cases, other parameters of hepatic function remained stable. No subject was assessed by the independent, hepatic expert panel as meeting criteria for Hy's law. There were no cases of DAA-related hepatic dysfunction or failure during this study, according to this panel.

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

Summary/Conclusions (Continued)

Conclusions:

Treatment with a 12- or 24-week regimen of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV resulted in SVR_{12} rates of 91.8% and 96.5%, respectively, which demonstrated both noninferiority and superiority to the historical control rate for telaprevir plus pegIFN and RBV therapy in HCV genotype 1-infected, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis. Further subgroup analyses suggest that the lower overall SVR_{12} rate of 91.8% for the 12-week regimen was attributable to the differential treatment response among HCV genotype 1a null responders. Therefore, based on prior treatment history, 12 weeks of treatment with the AbbVie 3-DAA + RBV regimen should be recommended for all HCV genotype 1 patients with compensated cirrhosis, with the exception of HCV genotype 1a prior null responders, for whom 24 weeks of treatment provides a higher SVR_{12} rate. With these recommended treatment durations, the overall SVR_{12} rate in the genotype 1-infected compensated cirrhotic population is expected to be approximately 95%. Patients with genotype 1a infection and baseline serum alpha fetoprotein < 20 ng/mL, platelet count $\geq 90 \times 10^9$/L, and serum albumin ≥ 35 g/L should be treated for 12 weeks. Patients with genotype 1a infection and baseline serum alpha fetoprotein ≥ 20 ng/mL, platelet count $< 90 \times 10^9$/L, or serum albumin < 35 g/L at baseline may be treated for 24 weeks in order to reduce the risk of relapse.

The regimens were generally well tolerated, with no clinically significant differences in safety profiles based on treatment duration. 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 of subjects without cirrhosis.

Date of Report: 21May2015