

Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: ABT-450, ritonavir, ABT-267, ABT-333, ribavirin	Volume:	
<p>Name of Active Ingredient:</p> <p>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</p> <p>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</p> <p>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</p> <p>ABT-333: Sodium 3-(3-tert-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1)</p> <p>Ribavirin: 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide</p>	Page:	
<p>Title of Study: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-II)</p>		

Investigator: Stefan Zeuzem, MD	
Study Sites: 76 investigative sites in Australia, Canada, Czech Republic, Denmark, France, Germany, Ireland, Italy, Mexico, The Netherlands, Portugal, Russia, Spain, United Kingdom, and the United States/Puerto Rico	
Publications: 1	
Studied Period (Years): First Subject First Visit: 14 November 2012 Last Subject Last Visit: 23 October 2014	Phase of Development: 3
<p>Objectives:</p> <p>The primary objectives of this study were to compare the percentage of subjects achieving sustained virologic response 12 weeks postdosing (SVR₁₂) (HCV RNA < lower limit of quantitation [LLOQ] 12 weeks following treatment) after 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 coadministered with RBV (the DAA combination regimen) to the historical SVR rate of telaprevir plus pegylated interferon (pegIFN) and RBV therapy and to assess the safety of the DAA combination regimen versus placebo for 12 weeks in pegIFN/RBV treatment-experienced HCV genotype 1-infected adults without cirrhosis.</p> <p>The secondary objectives of this study were to measure the effect of the DAA combination regimen compared with placebo for 12 weeks on normalizing alanine aminotransferase (ALT) levels and demonstrate the effect of the DAA combination regimen on SVR₁₂ in subjects with HCV genotype 1a and genotype 1b infection, and on HCV RNA levels during and after treatment as measured by on-treatment virologic failure and post-treatment (PT) relapse, respectively.</p>	
<p>Methodology:</p> <p>This was a Phase 3, randomized, double-blind (DB), placebo-controlled, multicenter study evaluating ABT-450/r/ABT-267 and ABT-333 coadministered with RBV in treatment-experienced, noncirrhotic HCV genotype 1-infected adults.</p> <p>Approximately 400 HCV genotype 1-infected, treatment-experienced adults were randomized to Arms A and B in a 3:1 ratio in the DB Treatment Period at approximately 80 sites.</p> <ul style="list-style-type: none"> • 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 (3-DAA + RBV); • Arm B: Placebo for ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + placebo for ABT-333 250 mg BID + placebo for RBV for 12 weeks followed by ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID + RBV for 12 weeks <p>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).</p> <p>The duration of the study was up to 72 weeks (not including a screening period of up to 35 days), consisting of 3 periods: the DB Treatment Period, the Open-Label (OL) Treatment Period (for subjects randomized to placebo treatment group), and the PT Period (for all subjects who received active study drugs).</p>	

Methodology (Continued):

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

- Null responder:
 - o 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
 - o 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 $\geq 2 \log_{10}$ IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment;
- 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.

In the DB Treatment Period, randomization was stratified by type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) and HCV subgenotype (1a versus non-1a). The number of relapsers to previous pegIFN/RBV treatment was limited to ≤ 120 subjects and the total number of partial responders plus relapsers to previous pegIFN/RBV treatment was limited to ≤ 300 subjects to ensure adequate representation in the presumed harder to treat null-responder population.

Subjects randomized to placebo treatment were administered open-label active study drugs for 12 weeks following the DB Treatment Period. All subjects administered active study drugs were to be followed for 48 weeks post-treatment to monitor for safety, HCV RNA, the emergence and/or persistence of resistant viral variants and assessment of patient-reported outcomes (PROs [not required for the placebo treatment group during the OL and PT Periods]).

The primary analysis, as described in this report, occurred after subjects initially randomized to active drug completed through PT Week 12 or prematurely discontinued the study and subjects who were initially randomized to placebo completed 12 weeks of OL active treatment or prematurely discontinued study drug. A follow-up analysis was performed after subjects who received OL active treatment completed through PT Week 12 or prematurely discontinued the study at a date to correspond with the 120-day Safety Update. All remaining data through PT Week 48 were summarized in the end-of-study analysis.

Safety evaluations occurred throughout the study by a Data Monitoring Committee. Throughout the DB Treatment Period, efficacy evaluations were conducted to evaluate if $\geq 50\%$ of null or partial responder subjects had experienced relapse after completing 3-DAA + RBV treatment, in which case a determination would be made as to whether treatment for those subjects remaining on study drug should be extended to 24 weeks. The treatment extension criteria were not met.

In addition, virologic stopping criteria were evaluated for individual subjects. If a subject met the virologic stopping criteria, i.e., experienced confirmed virologic failure, the investigator and sponsor were to be informed, the study drug assignment was to be unblinded and study drugs were to be discontinued.

Number of Subjects (Planned and Analyzed):

Approximately 400 subjects were planned to be enrolled; 394 subjects (297 in Arm A and 97 in Arm B) were enrolled and received at least 1 dose of study drug. Ninety-six (96) subjects in Arm B received open-label 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 ≥ 18 to < 38 kg/m². 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 were in a condition of general good health, other than the HCV infection. Subjects had a chronic HCV genotype-1 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	Abbott/AbbVie	Oral	Tablet	75 mg/ 50 mg/ 12.5 mg	12-005439 12-005575
ABT-450/r/ABT-267 placebo	Abbott/AbbVie	Oral	Tablet	0 mg	12-005189
ABT-333	Abbott/AbbVie	Oral	Tablet	250 mg	12-003125
ABT-333 placebo	Abbott/AbbVie	Oral	Tablet	0 mg	12-002404
RBV tablets	Kadmon Pharmaceuticals, LLC ^a	Oral	Tablet	200 mg	12-004860
	Roche Pharma AG	Oral	Tablet	200 mg	12-005353
	Roche Pharma AG	Oral	Tablet	200 mg	12-005411
RBV capsules	Overencapsulated by: [REDACTED] for Abbott/AbbVie ^b	Oral	Hard Gelatin Capsule	200 mg	12-004473 12-006205 12-005109 12-003965
Placebo for overencapsulated RBV	Abbott/AbbVie	Oral	Hard Gelatin Capsule	0 mg	10-004370 12-002308
<p>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.</p> <p>b. Ribavirin tablets were commercial product. RBV tablets used in overencapsulated lots 12-005109 and 12-003965 were manufactured by Roche Pharma AG. Ribavirin tablets used in overencapsulated lots 12-004473 and 12-006205 were manufactured by Kadmon Pharmaceuticals, LLC.</p>					
<p>Duration of Treatment: In the DB Treatment Period, subjects received ABT-450/r/ABT-267 and ABT-333 co-administered with RBV or matching placebos for 12 weeks. Subjects randomized to placebo in the DB Treatment Period received ABT-450/r/ABT-267 and ABT-333 co-administered with RBV for 12 weeks in the OL Treatment Period.</p>					
<p>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Reference therapy was placebo, as described above.</p>					

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

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). 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 collected at each study visit for Arm A subjects during DB Treatment Period and Arm B subjects during OL Treatment Period; 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:

The primary efficacy endpoints were:

- SVR₁₂: Noninferiority of the 3-DAA + RBV treatment group to the historical rate for telaprevir plus pegIFN and RBV; lower bound of 95% confidence interval (LCB) must have exceeded 60% to achieve noninferiority.
- SVR₁₂: Superiority of the 3-DAA + RBV treatment group to the historical rate for telaprevir plus pegIFN and RBV; LCB must have exceeded 70% to achieve superiority.

Statistical Methods (Continued)

Efficacy (Continued):

The following hypotheses were tested on subjects in the intent-to-treat (ITT) population who were randomized to active study drug (Arm A). To test the hypothesis that the percentage of treatment-experienced HCV genotype 1 infected subjects treated with ABT-450/r/ABT-267 + ABT-333 with RBV who achieved SVR₁₂ is noninferior or superior to the historical SVR rate for the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage and 2-sided 95% confidence interval (CI) of subjects with SVR₁₂ were calculated using the simple proportion and variance, and the normal approximation to the binomial distribution was used to estimate the CI. The LCB must have been > 60% in order for the regimen to be considered noninferior, and the LCB must have been > 70% in order for the regimen to be considered superior to the historical SVR rate in treatment-experienced HCV genotype 1 infected subjects without cirrhosis treated with telaprevir plus pegIFN and RBV.

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

1. ALT normalization rate during treatment in Arm A compared to Arm B.
2. Sustained virologic response 12 weeks postdosing (SVR₁₂): In HCV genotype 1a-infected subjects, for superiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV, the LCB must have exceeded 65%.
3. SVR₁₂: In HCV genotype 1b-infected subjects, for superiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV, the LCB must have exceeded 77%.

ALT normalization (final ALT ≤ the upper limit of normal [ULN] in the DB Treatment Period) was calculated for all subjects in the ITT population with ALT above the ULN at baseline. To test the hypothesis that the percentage of subjects in the active arm with ALT normalization is greater than the percentage of subjects in the placebo arm with ALT normalization at the Final DB Visit, the treatment groups were compared using Fisher's exact test. If superiority of the active arm is demonstrated with a *P* value ≤ 0.05, then the DAA combination regimen was considered a success for this endpoint. To test the hypothesis that the percentage of treatment-experienced HCV genotype 1a subjects treated in Arm A who achieved SVR₁₂ was superior to the historical SVR rate in the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with SVR₁₂ was calculated with a 2-sided 95% CI calculated using the normal approximation to the binomial distribution. The LCB must have been greater than 65% in order for the regimen to be a success for this endpoint. To test the hypothesis that the percentage of treatment-experienced HCV genotype 1b subjects treated in Arm A who achieved SVR₁₂ was superior to the historical SVR rate in the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with SVR₁₂ was calculated with a 2-sided 95% CI calculated using the normal approximation to the binomial distribution. The LCB must have been greater than 77% in order for the regimen to be a success for this endpoint.

Statistical Methods (Continued)

Resistance:

The following resistance information was analyzed for subjects receiving active 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/or 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 treatment arms using analysis of covariance models with a treatment group factor and the baseline score as a covariate.

The number and percentage of subjects without a decrease from baseline to the Final DB 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 calculated and compared between treatment arms. The MIDs for the HCV-PRO total score and the EQ-5D-5L health index are based on receiver operating characteristic (ROC) curve anchored by SF-36 Mental Component Summary and SF-36 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 for subjects in Arm A from the DB Treatment Period and Arm B from the OL Treatment Period.

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 active regimen and placebo during the DB Treatment Period using Fisher's exact test. Tabulations were also provided in which the number of subjects reporting an adverse event (MedDRA term) in each treatment group was additionally presented by rating (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 DB Treatment Period was summarized by treatment group and compared between treatment groups 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 DB Treatment Period were compared between treatment groups using Fisher's exact tests.

Summary/Conclusions

Efficacy Results:

The primary efficacy endpoints of noninferiority of the 3-DAA + RBV treatment group in Arm A to the historical comparator in SVR₁₂ was achieved by 286/297 (96.3%) subjects, with a 95% CI of 94.1% to 98.4%. The LCB was above 60% (noninferiority threshold) and above 70% (superiority threshold). Therefore, both primary endpoints were achieved. Only 2.4% of all 297 ITT subjects experienced true virologic failure (all of which were due to post-treatment relapse).

Sensitivity analyses that evaluated alternative methods to impute missing post-treatment virologic results were consistent with the primary analysis. A test of heterogeneity within the 3-DAA + RBV treatment group of Arm A indicated no significant heterogeneity ($P = 0.573$) across the randomization strata defined by previous pegIFN/RBV treatment response (null responder, partial responder, and relapser) and HCV subgenotype (1a versus non-1a). For all prespecified subgroups, the lower confidence bound for the SVR₁₂ rate was above the prespecified noninferiority threshold of 60%.

All 3 ranked secondary endpoints were achieved:

- A statistically significantly greater proportion of subjects randomized to 3-DAA + RBV (Arm A) achieved normalization of ALT during treatment compared with subjects randomized to placebo (96.9% versus 12.8%);
- For the HCV genotype 1a subgroup of Arm A, SVR₁₂ was achieved in 96.0% (95% CI 93.0% – 98.9%). The LCB was above the prespecified threshold of 65%, demonstrating superiority to the historical telaprevir-based SVR rate;
- For the HCV genotype 1b subgroup of Arm A, SVR₁₂ was achieved in 96.7% (95% CI 93.6% – 99.9%). The LCB was above the prespecified threshold of 77%, demonstrating superiority to the historical telaprevir-based SVR rate.

For HCV genotype 1-infected, pegIFN/RBV treatment-experienced adults without cirrhosis, noninferiority and superiority of 3-DAA + RBV (SVR₁₂ rate of 96.3%) to the historical control rate for telaprevir-based therapy were demonstrated for SVR₁₂ and only 2.4% of all ITT subjects in Arm A experienced true virologic failure (all post-treatment relapse). Superiority to the telaprevir-based control rate in subjects with the same HCV subgenotype was demonstrated for both genotype 1a (SVR₁₂ rate 96.0%) and genotype 1b (SVR₁₂ rate 96.7%).

The SVR₁₂ rates for subjects in Arm A who were prior pegIFN/RBV null responders, partial responders, and relapsers were 95.2%, 100%, and 95.3%, respectively.

Resistance Results:

Resistance analyses of subjects in the primary virologic failure (PVF) population comprised 7 subjects who were treated with active study drug during the DB Treatment Period (Arm A) and 2 subjects treated with active study drug in the OL Treatment Period (Arm B). There was no apparent association between baseline variants at signature resistance-associated amino acid positions and treatment outcome. The predominant variants in the genotype 1a-infected subjects in the PVF population at the time of failure were D168V in NS3, M28V and Q30R in NS5A, and S556G in NS5B. Of the 5 genotype 1a-infected subjects in the PVF population, 3 had no resistance-associated variants in NS5B at the time of virologic failure. The predominant variants in the single genotype 1b-infected subject who had resistance-associated variants at the time of failure were Y56H and D168A in NS3, Y93H in NS5A, and C316N + S556G in NS5B. Four of the 9 subjects in the PVF population had resistance-associated variants in all 3 targets (NS3, NS5A, and NS5B) at the time of failure.

Summary/Conclusions (Continued)

Resistance Results (Continued):

The 4 subjects in the non-PVF population that had post-baseline sequencing available had no resistance-associated variants in NS3 and NS5B at the time of treatment discontinuation. Both of the genotype 1a-infected subjects had variants at amino acid positions 28 and/or 30 in NS5A at the time of treatment discontinuation. One of the 2 genotype 1b-infected subjects had Y93H in NS5A at baseline and at the time of treatment discontinuation, while the other had no resistance-associated variants in NS5A.

Treatment-emergent resistance-associated variants were observed in NS3, NS5A, and NS5B in 6, 7, and 2 of the 9 subjects in the PVF population, respectively. Variants in NS3 in genotype 1a-infected subjects declined through PT Week 24 (2/4, 50%) and PT Week 48 (1/3, 33%). Treatment-emergent resistance-associated variants in NS5A in genotype 1a infected subjects remained detectable at similar levels through PT Week 48. Trends in persistence of variants in genotype 1b could not be determined due to the low number of subjects with virologic failure who had sequence data at follow-up time points.

Patient-Reported Outcomes Results:

More than half of subjects who were treated with 3-DAA + RBV in Arm A experienced decreases (that did not meet criteria to be considered of minimal importance) or increases from baseline in their HRQoL, function, and wellbeing (per SF-36v2 Mental Component Summary, Physical Component Summary, EQ-5D-5L Health Index Score, and HCV-PRO total scores) at the end of treatment. During the 12-week DB treatment period, the 3-DAA + RBV regimen had mild impact on patient HRQoL compared with placebo. Post-treatment HRQoL scores for 3-DAA + RBV showed improvement over baseline.

Pharmacokinetic Results:

Based on the binned trough plasma concentration values, the exposures achieved in HCV treatment-experienced subjects in the present study for DAAs, ritonavir, and RBV from the OL Treatment Period of Arm B were generally comparable with the exposures from the DB Treatment Period of Arm A.

Safety Results:

The 3-DAA + RBV regimen in Arm A was generally well tolerated, with few subjects (1.0%) prematurely discontinuing study drug because of treatment-emergent adverse events. A majority of subjects in the 3-DAA + RBV treatment group (91.6%) and the placebo treatment group (82.5%) experienced at least 1 treatment-emergent adverse event during the DB Treatment Period. However, most of these subjects experienced events that were mild in severity in both treatment groups.

The 2 most common treatment-emergent adverse events in the 3-DAA + RBV and placebo treatment groups during the DB Treatment Period were headache (36.4% and 35.1%, respectively) and fatigue (33.3% and 22.7%, respectively). The percentage of subjects with these events was not statistically significantly different between treatment groups. Of the treatment-emergent adverse events reported for $\geq 5.0\%$ of subjects in either treatment group, the events of pruritus, vomiting, and anemia occurred statistically significantly more frequently in the 3-DAA + RBV treatment group compared with the placebo treatment group.

The treatment-emergent adverse event profile for subjects receiving 3-DAA + RBV during the OL Treatment Period was similar to that of the 3-DAA + RBV treatment group during the DB Treatment Period. The most common treatment-emergent adverse events were headache, fatigue, asthenia, dyspnea, nausea, cough, pruritus, and insomnia.

Summary/Conclusions (Continued)

Safety Results (Continued):

No subject died during the study. Six subjects (2.0%) in the 3-DAA + RBV treatment group and 1 (1.0%) subject in the placebo treatment group experienced treatment-emergent serious adverse events during the DB Treatment Period. No commonality was evident among the reported events. In the 3-DAA + RBV treatment group during the DB Treatment Period, only one serious adverse event (preferred term: cerebrovascular accident) occurring in 1 (0.3%) subject was assessed by the investigator as having a reasonable possibility of being related to DAAs. In 2 (0.7%) subjects, the serious adverse events (preferred terms: cerebrovascular accident and renal failure acute) were considered as having a reasonable possibility of being related to RBV by the investigator.

While receiving 3-DAA + RBV during the OL Treatment Period, serious adverse events were reported by 3 (3.1%) subjects. Two of these events, bile duct stone and calculus ureteric, were considered by the investigator and AbbVie to have no reasonable possibility of relationship to DAA treatment. The event of calculus ureteric led to interruption of study drug. The third event, angioedema, was considered to have a reasonable possibility of relationship to DAA and to RBV treatment and led to premature discontinuation of the study drug regimen.

Three (1.0%) subjects in the 3-DAA + RBV treatment group and no subject in the placebo treatment group experienced at least 1 adverse event that led to premature discontinuation of study drug during the DB Treatment Period. Only 1 event (renal failure acute) was serious and no specific adverse event (preferred term) led to premature discontinuation of study drug for more than 1 subject. While receiving 3-DAA + RBV during the OL Treatment Period, 1 (1.0%) subject experienced a serious adverse event (angioedema) that led to premature discontinuation of study drug. No other subject prematurely discontinued study drug during the OL Treatment Period due to a treatment-emergent adverse event. The low rates of study drug discontinuation (1.0%) during 3-DAA + RBV treatment, whether during the DB or OL Treatment Periods, affirm the general tolerability of the 3-DAA + RBV treatment regimen.

Analyses of rash-related events, hemoglobin values and anemia-related events, liver function test values and hepatic-related events, and bilirubin-related events observed during this study showed no new or different pattern compared with other clinical trials of AbbVie DAAs with RBV.

During the DB Treatment Period, a similar percentage of subjects in the 3-DAA + RBV treatment group compared with the placebo treatment group experienced at least 1 adverse event that met the drug-induced rash company MedDRA query (CMQ) during the DB Treatment Period, the most common of which were pruritus and rash. Most of these events were mild and no subject experienced a treatment-emergent adverse event that met the severe cutaneous reactions standardized MedDRA query. A similar percentage of subjects administered 3-DAA + RBV during the OL Treatment Period experienced a treatment-emergent adverse event that met the drug-induced rash CMQ.

Reductions in hemoglobin were observed in the 3-DAA + RBV treatment group, as evidenced by a mean -25.2 g/L decrease from baseline to the Final DB Treatment Period Visit. Postbaseline grade 2 hemoglobin values occurred in 4.7% of subjects who received the 3-DAA + RBV regimen during the DB Treatment Period; 1 subject had a postbaseline grade 3 hemoglobin value and no subject had a grade 4 value. The event of anemia was reported in a similarly low (5.4%) number of subjects. No subject received a blood transfusion or erythropoietin. Moreover, by PT Week 4, the mean hemoglobin for the 3-DAA + RBV treatment group had returned to near baseline levels. Similarly, 2.1% of subjects who received the 3-DAA + RBV regimen in the OL Treatment Period experienced grade 2 hemoglobin levels.

Summary/Conclusions (Continued)

Safety Results (Continued):

With regard to bilirubin, 2.4% of subjects in the 3-DAA + RBV treatment group experienced an elevation in total bilirubin $> 3 \times$ ULN; few subjects experienced events of jaundice (2.0%) or scleral icterus (0.3%). There were no 3-DAA + RBV interruptions or discontinuations due to elevations in total bilirubin. A similarly low percentage (5.2%) of subjects administered 3-DAA + RBV in the OL Treatment Period experienced total bilirubin elevations $> 3 \times$ ULN.

During the DB Treatment Period 5 (1.7%) subjects who received the 3-DAA + RBV regimen had at least grade 3 ALT elevations during treatment; in 2 of these subjects, the ALT levels normalized after discontinuation of the oral combination hormonal contraceptive Eugynon. Three subjects were categorized as being in the Hy's Law quadrant of an evaluation of drug-induced serious hepatotoxicity (eDISH) plot but none was assessed as meeting criteria consistent with Hy's Law by the blinded external hepatic panel. Two of these subjects completed study drug with ALT levels that were within the normal range. The third subject discontinued study drug due to a treatment-emergent adverse event of transaminases increased. At discontinuation, the ALT level was lower and the bilirubin level had declined to within normal limits. Follow-up testing at Day 193 after discontinuation of study drug showed ALT and total bilirubin levels that were within the normal range. In the OL Treatment Period, 3 (3.1%) subjects who received the 3-DAA + RBV regimen had at least grade 3 ALT elevations. Two subjects were categorized as being in the Hy's Law quadrant of an eDISH plot, but neither was assessed as meeting criteria for Hy's Law by the blinded external hepatic panel.

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 coadministered with RBV in HCV genotype 1-infected, treatment-experienced, noncirrhotic adults showed an SVR₁₂ rate of 96.3%, which demonstrated both noninferiority and superiority to the historical control rate for telaprevir plus pegIFN and RBV in HCV genotype 1-infected adults without cirrhosis. There were no changes to the overall conclusions from the interim CSR. Only 2.4% of all ITT subjects experienced virologic failure during or post-treatment. The 12-week regimen of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV was generally well tolerated in HCV genotype 1-infected, treatment-experienced adults, with only 1.0% of subjects discontinuing study drug as a consequence 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.

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