

Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: ABT-267, ABT-450, ritonavir, ABT-333, ribavirin	Volume: Page:	
Name of Active Ingredient: 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-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: 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, [5S-(5R*,8R*,10R*,11R*)] ABT-333: (sodium N-{6-[3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl]naphthalen-2-yl}methanesulfonamide) Ribavirin: 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide		

<p>Title of Study: A Randomized, Open-Label, Multicenter Study to Evaluate the Antiviral Activity, Safety, and Pharmacokinetics, of ABT-450 with Ritonavir (ABT-450/r) in combination with ABT-267 and/or ABT-333 With and Without Ribavirin (RBV) for 8, 12 or 24 Weeks in Treatment-Naïve and Null Responder Subjects with Genotype 1 Chronic Hepatitis C Virus Infection</p>	
<p>Coordinating Investigator: Kris V. Kowdley, MD</p>	
<p>Study Sites: 92 investigative sites in United States, Puerto Rico, Canada, France, Germany, Spain, United Kingdom, Australia and New Zealand.</p>	
<p>Publications: 12 abstracts</p>	
<p>Studied Period (Years): First Subject First Visit: 03 October 2011 Last Subject Last Visit: 19 September 2013</p>	<p>Phase of Development: 2</p>
<p>Objectives: The primary objectives of this study were to assess the safety of all treatment regimens, and to compare the percentage of subjects achieving 24-week sustained virologic response (SVR₂₄) (hepatitis C virus [HCV RNA] < lower limit of quantitation [LLOQ] at post-treatment Week 24) following 8 weeks of treatment with 3 direct-acting antiviral agents (DAAs) and RBV versus 12 weeks of treatment with 3 DAAs and RBV in HCV genotype 1-infected treatment-naïve adults. The secondary objectives of this study were to compare the percentage of subjects achieving SVR₂₄,</p> <ul style="list-style-type: none"> • who had been treated with 3 DAAs with RBV for 8 versus 24 weeks (treatment-naïve subjects) and for 12 weeks versus 24 weeks (treatment-naïve and null responder subjects); • who had been treated with 2 DAAs (ABT-450/r and ABT-333) with RBV for 12 weeks versus 3 DAAs with RBV for 12 weeks (treatment-naïve subjects); • who had been treated with 2 DAAs (ABT-450/r and ABT-267) with RBV for 12 weeks versus 3 DAAs with RBV for 12 weeks (treatment-naïve and null responder subjects); • who had been treated with 3 DAAs with RBV for 12 weeks versus 3 DAAs without RBV for 12 weeks (treatment-naïve subjects); • among treatment-naïve versus null responder subjects who had been treated with 3 DAAs with RBV for 12 or 24 weeks at different doses of ABT-450/r (100/100 mg, 150/100 mg); and • to examine any emerged or enriched mutations postbaseline by mixed population and/or clonal sequencing. 	

Methodology:

This was a Phase 2, open-label, randomized, combination treatment study of multiple doses of ABT-450/r, and ABT-267 and/or ABT-333 with or without RBV in HCV genotype 1-infected treatment-naïve subjects and previous null responders to pegylated interferon (pegIFN) and RBV treatment.

The study consisted of a Treatment Period of 8, 12, or 24 weeks and a Follow-up Period for sustained viral response and resistance monitoring for 48 weeks. Screening evaluations were to be completed within 35 days of the first dose of study drug. There were a total of 14 treatment groups consisting of approximately 20 to 80 subjects in each group. Randomization within each population of subjects was stratified by interleukin 28B (IL28B) genotype (CC, non-C/C) and HCV subtype (1a, non-1a).

Plasma samples for pharmacokinetic analysis were collected on Day 1 up to 4 hours post dose. Subjects returned to the study site on an outpatient basis on Day 3 for additional pharmacokinetic sampling and other study procedures (e.g., adverse event assessment, resistance monitoring, and HCV RNA testing). Subjects continued to return to the site on an outpatient basis up to Weeks 8, 12, or 24 for resistance monitoring, HCV RNA testing, and assessment of the safety and tolerability of the treatments.

Patient-Reported Outcomes (PROs) were also assessed at specified visits. Ongoing review of the data was planned in order to determine if subjects met the stopping criteria.

All subjects who received at least 1 dose of DAA, regardless of whether they prematurely discontinued or completed the study were monitored for viral response and resistance on an outpatient basis for an additional 48 weeks after the last dose of DAA. All subjects who received at least 1 dose of DAA and who failed to achieve virologic suppression, or who experienced virologic breakthrough on DAA therapy or relapse post DAA therapy, were offered pegIFN and RBV for up to 48 weeks, if considered medically appropriate by the investigator.

Number of Subjects (Planned and Analyzed):

Approximately 560 subjects were planned. Five hundred seventy-one subjects received at least 1 dose of study drug and were analyzed.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV-infected, treatment-naïve or prior null responders to pegIFN plus RBV 18 to 70 years of age, inclusive, with a body mass index (BMI) ≥ 18 to < 38 kg/m². Females were either postmenopausal for at least 2 years, surgically sterile, or practicing birth control. Male subjects and/or partner(s) had to be practicing at least 2 effective methods of birth control. Subjects had a chronic HCV genotype 1 infection for at least 6 months prior to study enrollment; Fibro Test score ≤ 0.72 and aspartate aminotransferase (AST) to platelet ratio index ≤ 2 at screening or FibroScan[®] result of < 9.6 kPa or the absence of cirrhosis based on a liver biopsy within the last 36 months.

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	AbbVie/Abbott	Oral	Tablet	50 mg	10-003507 11-000781
Ritonavir	AbbVie/Abbott	Oral	Soft Gelatin Capsule	100 mg	10-004021 11-005228 12-000721 11-004372 11-004374
ABT-267	AbbVie/Abbott	Oral	Tablet	25 mg	11-000867 11-002033 11-002816
ABT-333	AbbVie/Abbott	Oral	Tablet	400 mg	11-000511 11-000512 11-002720 11-005348
RBV	Patheon Inc. for Roche Latvija SIA or Cadila Healthcare Ltd for Zydus Pharmaceuticals USA Inc.	Oral	Tablet	200 mg	11-002499 ^a 11-002516 ^a 11-002497 ^a 11-003639 ^a 11-002588 ^b 11-002262 ^b 10-005342 ^b 10-005338 ^b
<p>a. Manufactured by Cadila. b. Manufactured by Patheon.</p> <p>Duration of Treatment: Study drug (ABT-450/r, ABT-267, and/or ABT-333, with or without RBV) was administered for 8, 12, or 24 weeks, according to the assigned treatment group.</p> <p>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Not applicable.</p>					

Criteria for Evaluation

Efficacy:

The primary efficacy endpoint was the comparison of the percentage of subjects with SVR₂₄ (HCV RNA < LLOQ in the SVR₂₄ window [24 weeks after the last actual dose of study drug]) between the treatment-naïve subjects following 8 weeks of treatment with 3 DAAs (with ABT-450/r 150/100 mg) and RBV and those with 12 weeks of treatment with 3 DAAs (with ABT-450/r 150/100 mg) and RBV (Group A versus Group G). The secondary efficacy endpoints were comparisons of the percentage of subjects with SVR₂₄ between treatment groups and pooled treatment groups, as appropriate, to evaluate duration of treatment, comparison of naïve versus null responder subjects, comparison of ABT-450 doses, the contribution of ABT-267 and ABT-333, and the contribution of RBV; other prespecified pairwise comparisons examined the same concepts. SVR₁₂ (HCV RNA < LLOQ in the SVR₁₂ window [12 weeks after the last actual dose of study drug]) was also analyzed as an efficacy endpoint. Additional efficacy endpoints included rapid virologic response (RVR, HCV RNA < LLOQ at Week 4), end-of-treatment response (EOTR, HCV RNA < LLOQ at the end of 8, 12, or 24 weeks of treatment), and SVR₄ (HCV RNA < LLOQ in the SVR₄ window [4 weeks after the last actual dose of active study drug]).

Resistance:

The resistance endpoints were: the fold change from baseline and reference HCV samples in the half-maximal effective concentration (EC₅₀) at various time points; mutations at each amino acid position by population and/or clonal nucleotide sequencing compared with baseline and prototypic sequences; and development and persistence of viral resistance with various treatment regimens.

Pharmacokinetic:

Plasma concentrations for ABT-450, ABT-267, ABT-333, ABT-333 M1 metabolite, ritonavir, and RBV were summarized.

Safety:

Safety was evaluated based on adverse events, clinical laboratory determinations, and vital signs.

Statistical Methods

Efficacy:

Logistic regression with treatment group, baseline log₁₀ HCV RNA level, HCV subgenotype (1a or non-1a), geographic regions and IL28B genotype (CC, non-CC) as predictors was used to compare the groups for SVR₂₄ rates. Secondary efficacy analyses and additional comparisons of the percentage of subjects with SVR₂₄, RVR, early virologic response, EOTR, and SVR₁₂ used logistic regression with treatment group, baseline log₁₀ HCV RNA level, HCV subgenotype (1a or non-1a), geographic region, IL28B genotype (CC, non-CC), and ABT-450/r dose and subject populations (treatment-naïve versus null responder, if appropriate) as predictors. The stratum-adjusted Mantel-Haenszel (MH) method controlling for the baseline stratification variables (IL28B genotype [CC and non-CC] and HCV subgenotype [1a and non-1a]) was also applied for the comparisons of RVR, EOTR, and all SVR rates among the specified groups.

Statistical Methods (Continued)

Resistance:

The following was summarized for all subjects: the variants at signature resistance-associated amino acid positions by nucleotide population sequencing at baseline compared with the appropriate prototypic reference sequence for each DAA target (nonstructural protein 3 [NS3], nonstructural protein 5A [NS5A], and/or nonstructural protein 5B [NS5B]).

The following was summarized for the subjects who did not achieve SVR (due to virologic failure or for reasons other than virologic failure and who had HCV RNA \geq 1000 IU/mL): the variants at each amino acid position for each postbaseline time point that was analyzed by nucleotide population and/or clonal sequencing compared with baseline and the appropriate prototypic reference sequences.

A summary by baseline variants at signature positions of all available subjects.

The persistence of resistance-associated substitutions that emerged for each target (NS3, NS5A, and/or NS5B) was assessed by population sequencing at Post-Treatment Weeks 24 and 48.

The fold change in EC₅₀ level at baseline for each DAA target (NS3, NS5A, and/or NS5B) was compared with the appropriate prototypic standard and the fold change in EC₅₀ level at each postbaseline time point that was analyzed for each DAA target was compared with baseline and the appropriate prototypic standard. The fold changes at each time point were summarized for each treatment group with mean, standard error, median, minimum and maximum.

Pharmacokinetic:

Plasma concentrations of ABT-450, ABT-267, ABT-333, ABT-333 M1 metabolite, ritonavir, and RBV were tabulated for each subject and group. Summary statistics were computed based on visit and time after dose.

The plasma concentration data after Week 2 for all study groups were also summarized based on time after the last dose at each visit, by binning of the concentrations in different time intervals based on time after the last dose.

Safety:

All subjects who received at least 1 dose of DAA study medication were included in the safety analyses.

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA[®]), version 16.0. The number and percentage of subjects in each treatment group with treatment-emergent adverse events were tabulated by primary system organ class and MedDRA preferred term. The tabulation of the number of subjects with treatment-emergent adverse events also was provided with further categorization by severity rating and relationship to study drug. Comparisons of the percentage of subjects experiencing a treatment-emergent adverse event among the same treatment groups as compared for the additional efficacy endpoints were performed using Fisher's exact tests.

The company MedDRA query (CMQ) of drug-induced rash events was used to identify any rash events within this study. Adverse events related to the gallbladder were identified using the gallbladder-related disorders standardized MedDRA query (SMQ).

Statistical Methods (Continued)

Safety (Continued):

Clinical laboratory tests were summarized at each visit. The baseline value was the last measurement prior to the initial dose of study drug. Mean changes from baseline to each postbaseline visit were summarized for each treatment group. Laboratory data values were categorized as low, normal, or high based on reference ranges of the laboratory used in this study. The number and percentage of subjects in each treatment group who experience postbaseline shifts in clinical laboratory values from low/normal to high and high/normal to low based on the normal range were summarized. In addition, the number and percentage of subjects in each treatment group with postbaseline values meeting prespecified criteria for potentially clinically significant (PCS) laboratory values were summarized. Summaries of alanine aminotransferase (ALT), aspartate aminotransferase, alkaline phosphatase, and total bilirubin by maximum Common Terminology Criteria for Adverse Events (CTCAE) were also generated.

Mean changes in temperature, sitting systolic blood pressure, sitting diastolic blood pressure, sitting pulse rate, and weight from baseline to each postbaseline visit were summarized descriptively for each treatment group. Treatment group differences for mean changes from baseline and from Final Treatment Visit were analyzed and compared among the same treatment groups as compared for the additional efficacy endpoints using analysis of variance with treatment group as the factor. The between-group mean change from baseline with the 95% confidence interval, standard error, and *P* value were presented. Frequencies and percentages of subjects in each treatment group with postbaseline values meeting predefined criteria for PCS vital signs values were summarized. Comparisons of the percentage of subjects experiencing a value meeting the criteria among the same treatment groups as compared for the additional efficacy endpoints were performed using Fisher's exact tests.

Summary/Conclusions

Efficacy Results:

SVR₂₄ was achieved in 89.7% of treatment-naïve subjects and 92.5% of prior null responders overall. In both populations, the numerically highest SVR₂₄ rate was seen among subjects treated with 3 DAAs + RBV for a minimum of 12 weeks. Among subjects receiving 3 DAAs + RBV for at least 12 weeks, the SVR₂₄ rates for treatment-naïve subjects and null responders were 93.7% and 94.3% respectively (*P* = 0.825). Although differences in SVR₂₄ rates between treatment groups did not reach statistical significance for any individual comparison, these analyses were consistent in identifying the 3-DAA + RBV regimen as having the greatest efficacy among the regimens studied, thus supporting its advancement into Phase 3 studies.

Identification of Optimal Treatment Duration

The primary efficacy objective of this study was to compare the percentage of subjects achieving SVR₂₄ following 8 weeks of treatment with 3 DAAs (ABT-450/r at 150/100 mg) and RBV versus 12 weeks of treatment with 3 DAAs (ABT-450/r at 150/100 mg) and RBV in HCV genotype 1-infected treatment-naïve adults (Group A versus Group G). The respective SVR₂₄ rates for the 2 groups were 87.5% and 95.0%. While this difference did not reach statistical significance, the preponderance of the evidence favors a 12-week duration of treatment compared with 8 weeks.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

By contrast, no significant differences in efficacy were seen when 3 DAAs + RBV were given for 12 weeks compared with 24 weeks, either in treatment-naïve subjects or in prior null responders. The rate of relapse was low among subjects receiving 3 DAAs + RBV in the 12-week treatment groups (1 in the naïve cohort and 0 in the null responder cohort), and was not improved by an additional 12 weeks of treatment, suggesting that in this study, 24 weeks offered no efficacy advantage over 12 weeks regardless of prior treatment experience. While the SVR₁₂ and SVR₂₄ rates in the null responders treated for 24 weeks were numerically greater than in those treated for 12 weeks, all the treatment failures in the 12- and 24-week treatment arms were on-treatment viral breakthroughs, which would not have been prevented by a longer treatment duration.

Selection of Optimal Dose

No significant differences were seen in SVR₁₂ or SVR₂₄ rates among subjects treated with the same regimen, but with different ABT-450/r doses (100/100 mg versus 150/100 mg or 100/100 mg versus 200/100 mg). Overall efficacy was therefore not a driver of dose selection for Phase 3. Instead, selection of the ABT-450/r dose was based on resistance and safety analyses.

Selection of Optimal Regimen: The Contribution of ABT-267

Pairwise comparisons among treatment-naïve subjects receiving ABT-450/r + ABT-333 + RBV either with (Groups F and G) or without (Group B) ABT-267 consistently favor regimens containing ABT-267. The SVR₂₄ rates for Groups [F + G] and Group B were 96.2% and 82.9% ($P = 0.056$) and the SVR₁₂ rates were 98.7% and 85.4% ($P = 0.041$), suggesting that ABT-267 contributes to the efficacy of the regimen. The contribution of ABT-267 in null responders was not assessed in this study.

Selection of Optimal Regimen: The Contribution of ABT-333

The contribution of ABT-333 was assessed by pairwise comparisons both among treatment-naïve subjects (Groups [C + D] versus Groups [F + G]) and null responders (Group J versus Groups [K + L]). Comparison of regimens with identical ABT-450/r doses (Group C versus Group F) demonstrated an advantage for the ABT-333-containing regimen (84.6% versus 97.4%, $P = 0.090$), but had limited power to detect a true difference. Pooling treatment groups improves statistical power, but is complicated by differences in ABT-450/r dose (100/100 mg in Groups C and F, 150/100 mg in Group G, 200/100 mg in Groups D and J), which might confound the comparison. However, any bias in efficacy resulting from ABT-450/r dose would tend to favor the higher dose; thus, a finding of higher efficacy in the presence of ABT-333 and a lower dose of ABT-450/r is likely to reflect a true contribution of ABT-333. Analyses comparing pooled treatment groups consistently favored the ABT-333-containing regimens.

Selection of Optimal Regimen: Contribution of RBV

Multiple pairwise comparisons among treatment-naïve subjects between 12-week treatment groups receiving 3 DAAs without RBV (Group E) and those receiving 3 DAAs with RBV favor the regimen containing RBV. The comparison between Group E and Groups [F + G] shows SVR₁₂ rates of 91.1% and 98.7% ($P = 0.061$) and SVR₂₄ rates of 88.6% and 96.2% ($P = 0.089$) favoring the RBV-containing regimen.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Virologic Failure

Among treatment-naïve subjects, most on-treatment virologic failure occurred in the regimens without 1 component of the 3-DAA + RBV regimen: 1 subject in each of Groups B, [C + D], and E. Among null responders, 6.7% of subjects in Groups [K + L], and 2.3% of subjects in Group [M + N] experienced on-treatment virologic failure. No subject with HCV genotype 1b experienced on-treatment virologic failure.

Among treatment naïve subjects completing treatment, most relapses during or before the SVR₁₂ window occurred in the 8-week treatment group or in regimens without 1 component of the 3-DAA + RBV regimen: 11.3% of subjects in Group A, 7.9% of subjects in Group B, 6.6% of subjects in Groups [C + D], 1.3% in Groups [F + G], and none in Groups [H + I]. Similarly, among null responder subjects, 11.4% of subjects in Group J, no subjects in Groups [K + L], and no subjects in Groups [M + N] experienced relapses during or before the SVR₁₂ window. One (1.3%) additional subject in Group A and 2 (2.6%) subjects in Groups [C + D] experienced relapse in the SVR₂₄ window, and 1 (1.5%) subject in Groups [H + I] experienced relapse after the SVR₂₄ window.

Subgroup Analyses

Subgroup analyses demonstrated high SVR₂₄ rates regardless of IL28B genotype, HCV subtype, race, or baseline HCV RNA level. A lower percentage of subjects with fibrosis stage \geq F3 achieved SVR₂₄, especially in the 8-week treatment group and the treatment groups that received only 2 DAAs (i.e., without ABT-333 or ABT-267). In addition, higher percentages of females versus males and of subjects with genotype 1b versus subjects with HCV genotype 1a achieved SVR₂₄ in the majority of treatment groups. The impact of these baseline characteristics on treatment response will be evaluated more fully in Phase 3 studies. No subject with HCV genotype 1b experienced on-treatment virologic failure. This finding suggests that the full regimen of 3 DAAs + RBV may not be necessary in the population of genotype 1b-infected patients, and supports evaluation of a regimen with fewer agents in Phase 3 studies in some populations.

Agreement Between Efficacy Measures of HCV RNA

Nearly all subjects (> 95%) in each treatment group achieved the additional efficacy endpoints of RVR and EOTR. SVR₄ rates were similar to SVR₁₂, with 99.0% agreement and positive and negative predictive values of SVR₄ on SVR₁₂ of 98.9% and 100.0%, respectively. The agreement between SVR₁₂ and SVR₂₄ was 98.3%, and the positive and negative predictive values of SVR₁₂ on SVR₂₄ were 98.1% and 100.0%, respectively.

Resistance Results:

Prevalence of pre-existing variants at resistance-associated amino acid positions in NS3, NS5A, or NS5B was evaluated in baseline samples from over 315 genotype 1a- and 169 genotype 1b-infected subjects. No specific baseline resistance-associated variant appeared to be associated with an increased risk of virologic failure.

The majority of subjects randomized to the 8-week treatment group (Group A) who subsequently relapsed did not show emergence of resistance-associated variants in NS3, NS5A, or NS5B. In contrast, most subjects who experienced rebound on treatment or relapse after 12 weeks or longer of treatment showed emergence of previously described variants selected by the agents to which they were exposed.

Summary/Conclusions (Continued)

Resistance Results (Continued):

The most prevalent variants that emerged in NS3 at the time of virologic failure in genotype 1a-infected subjects were V36A/M + R155K, V36A/M + Y56H + D168V, Y56H + D168V, R155K, D168A, D168V, and D168Y. R155K alone or in combination with V36A or V36M was observed primarily in subjects receiving a regimen containing 100 mg of ABT-450, indicating that the R155K variants may be suppressed at higher doses of ABT-450. Of the common variants seen at the time of virologic failure in NS3, the frequency of D168V declined from 51.4% to 14.7% by Post-Treatment Week 24, and D168V was not detected at Post-Treatment Week 48. The R155K variant persisted at the Post-Treatment Weeks 24 and 48 time points. The most prevalent variants that emerged in NS5A at the time of virologic failure in genotype 1a-infected subjects were M28T, M28V, Q30R, and Y93N; and in NS5B were M414T and S556G. The NS5A and NS5B variants persisted from the time of virologic failure at approximately the same frequency at Post-Treatment Week 24 and 48 time points. RBV-associated NS5B polymorphisms T390I and F415Y did not emerge at the time of virologic failure in any subject.

Pharmacokinetic Results:

A supra-proportional increase in ABT-450 concentrations was observed with an increase in ABT-450/r dose. The DAA, ritonavir, and RBV concentrations were comparable between treatment-naïve and treatment-experienced HCV-infected subjects. RBV dosing does not appear to affect the concentrations of the DAAs and ritonavir.

PRO Results:

Patient reported responses measured by Short-Form 36, version 2 health survey (SF-36v2), EuroQol-5 Dimensions-5 Level (EQ-5D-5L), and HCV Patient-Reported Outcomes (HCV-PRO) did not significantly decline to end of treatment. SF-36v2 component summary and HCV-PRO total scores were improved over baseline at Post-Treatment Week 24.

Safety Results:

The safety population included all randomized subjects who received at least 1 dose of study drug (N = 571) and consisted of 438 treatment naïve subjects and 133 null responder subjects.

A majority of treatment-naïve subjects (89.0%) and null responder subjects (88.7%) experienced at least 1 treatment-emergent adverse event. Most subjects experienced 1 or more treatment-emergent adverse events that were mild or moderate in intensity and few experienced events that were severe in intensity (3.9% treatment-naïve, 2.3% null responders). All of the regimens studied were generally well tolerated, as evidenced by the low frequency of severe or serious treatment-emergent adverse events and the low incidence of subjects discontinuing study drug due to treatment-emergent adverse events.

The most common treatment-emergent adverse events in treatment-naïve subjects and null responder subjects were fatigue (30.1% and 24.8%, respectively) and headache (29.2% and 31.6%, respectively). The adverse event profile across all treatment arms is comparable to that seen in previous studies with ABT-450/r in combination with other DAAs and RBV.

In general, a comparable adverse event profile was seen across all pairwise comparisons of interest. A greater incidence of treatment-emergent adverse events was observed for the 24-week versus the 12-week 3-DAA + RBV study drug regimens, and a greater incidence of insomnia was observed in RBV-containing 3-DAA regimens compared with the regimen without RBV.

Summary/Conclusions (Continued)

Safety Results (Continued):

No treatment-emergent deaths were reported during the study. Three subjects died > 60 days after the last dose of study drug due to events considered not related or probably not related to DAA treatment. Eight subjects (1.4%) experienced serious adverse events during the study, of which, 1 (arthralgia) was considered possibly study-drug related by the investigator.

Nine subjects (1.6%) experienced at least 1 treatment-emergent adverse event that led to premature discontinuation of study drug. No specific adverse event (preferred term) led to premature discontinuation of study drug for more than 1 subject.

Adverse events of special interest included gallbladder-related and rash-related events. These events were selected based on the potential for DAA-related safety issues (cholecystitis) or based on safety issues (rash) identified for RBV and for other therapeutic agents for HCV. Gallbladder-related adverse events were evaluated using a standardized SMQ and rash-related adverse events were evaluated using an AbbVie CMQ. Three subjects (0.5%) experienced at least 1 treatment-emergent adverse event that met the gallbladder-related disorders SMQ, none of which was considered related to DAA treatment by the investigator. Thus, the findings from this study do not suggest an association with gallbladder-related events.

Regarding cutaneous adverse events, 155 subjects experienced at least 1 treatment-emergent adverse event that met the drug-induced rash CMQ. The most common events in both treatment-naïve subjects and null responder subjects were rash, pruritus, and pruritus generalized. These were generally mild, with the majority being assessed as either possibly or probably related to DAA and/or RBV treatment by the investigator. One subject had a treatment-emergent adverse event of pruritus generalized that led to discontinuation of study drug. Hence, the study drug regimens were not associated with severe or life-threatening rash events. Rash and pruritus are well-known adverse events associated with RBV, and an association with RBV is suggested by the numerically lower number of subjects with events meeting this CMQ in the group that did not receive RBV. Larger studies of DAA regimens with and without RBV will be required to confirm what proportion of these cutaneous adverse events might be attributable to the DAAs.

Laboratory parameters of special interest included hemoglobin, absolute neutrophil count, and liver function tests.

Anemia is a well-recognized RBV-related toxicity and has been described with the marketed HCV DAAs boceprevir and telaprevir. The percentages of subjects who experienced at least a grade 2 hemoglobin value in this study were small in all treatment groups, and no subject experienced a grade 3 or 4 hemoglobin value. Two subjects prematurely discontinued study drug due to a treatment-emergent adverse event of anemia or hemoglobin decreased. Since hemolytic anemia is a characteristic toxicity of RBV, larger studies of DAA regimens both with and without RBV will be required to confirm how much impact the DAA combination itself has on hemoglobin levels.

Neutropenia was considered a laboratory abnormality of interest on the basis of findings from a previous study in which the DAAs were administered with pegIFN. Findings from the current study suggest that the DAA regimens are not associated with decreases in neutrophil counts in the absence of interferon.

Summary/Conclusions (Continued)

Safety Results (Continued):

Asymptomatic elevations in serum ALT have been observed with the 3-DAA regimen prior to conducting Phase 3 clinical trials; therefore, characterization of this abnormality has been an important aspect of clinical development. In addition, ABT-450 is a known inhibitor of the organic anion transporting polypeptide 1B1 (OATP1B1) bilirubin transporter, and transient increases in total bilirubin (predominantly indirect bilirubin) have been observed with ABT-450 administration.

Hyperbilirubinemia could also be related to hemolysis, which is known to occur with RBV.

Mean ALT and AST values decreased in all groups, consistent with improvement in hepatocellular injury associated with decreased HCV replication. Asymptomatic grade 3 ALT elevations were observed in 6 subjects (1.1%), including 1 subject whose ALT level was decreasing from baseline but still grade 3 at Day 3. These elevations all resolved without intervention and none led to interruption or discontinuation of study drug treatment. None of the cases met the criteria for Hy's Law. The frequency of grade 3 ALT elevations after a postbaseline nadir was greater in subjects who received ABT-450/r at a dose of 200/100 mg (4/85, 4.7%) than in those who received a dose of 150/100 mg (1/322, 0.3%) or 100/100 mg (1/164, 0.6%), suggesting an association with ABT-450 exposure; no other risk factor was identified.

These findings suggest that an ABT-450/r dose < 200/100 mg daily may be associated with a lower rate of grade 3 ALT elevation. Four subjects had ALT values in Temple's quadrant (with maximum total bilirubin < 2 × upper limit of normal [ULN]) and 2 subjects had values in Hy's quadrant (with maximum total bilirubin ≥ 2 × ULN); none of these subjects were assessed as a potential Hy's law case.

Mean total bilirubin levels increased from baseline in all treatment groups at Week 1 and improved thereafter. The Week 1 elevation was smaller in the treatment group that did not receive RBV, suggesting that hyperbilirubinemia is mediated both by transporter inhibition due to ABT-450 and by hemolysis due to RBV. Of 11 subjects who experienced grade 3 total bilirubin levels while on treatment, 4 had an associated symptomatic treatment-emergent adverse event and 2 discontinued or interrupted study drug. Most of these elevations occurred during the first 15 days and decreased with ongoing treatment.

Alkaline phosphatase values remained near baseline for the duration of the study, with no evidence that study drug administration was associated with clinically meaningful changes.

Among the remaining hematology (other than hemoglobin and absolute neutrophil count) and chemistry parameters (other than liver function tests), mean changes were small and not clinically significant.

Review of urinalysis, vital signs, and electrocardiogram results did not demonstrate differences that were considered to be clinically meaningful.

Conclusions:

Regimens containing ABT-450/r with ABT-267 and/or ABT-333 with or without RBV were generally well tolerated, with low rates of discontinuations due to adverse events in HCV genotype 1-infected treatment-naïve subjects and previous null responder subjects without cirrhosis. The majority of subjects achieved SVR₂₄ with all regimens studied. The regimen of ABT-450/r, ABT-267, ABT-333, and RBV achieved the numerically highest SVR₁₂ and SVR₂₄ rates in both treatment-naïve and null responder cohorts. Twelve weeks of treatment provided the maximum likelihood of achieving SVR and there was no increase in SVR rate when treatment was extended from 12 to 24 weeks. Comparable efficacy was seen with all doses of ABT-450/r studied, but resistance analysis suggests an ABT-450/r dose of 150/100 mg or greater may be more efficacious at suppressing the R155K variant.

Subgroup analyses show few consistent trends or predictors of treatment failure, but genotype 1b infection appears to be consistently associated with higher efficacy regardless of the treatment regimen studied, including the regimen without RBV.

All regimens were associated with a low rate of serious adverse events or events leading to treatment discontinuation. The safety profiles of the regimens were similar in treatment-naïve and treatment-experienced subjects. A low rate of asymptomatic grade 3 ALT elevations was seen, which may be more frequent when ABT-450/r is dosed at 200/100 mg daily. No meaningful differences in safety or tolerability were seen when ABT-333 or ABT-267 were not in the regimen, but absence of RBV was associated with lower rates of several adverse events and less hemoglobin decrease. For populations that might be successfully treated with fewer antiviral agents, such as subjects infected with genotype 1b, it is therefore reasonable to study a regimen without RBV.

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