2.0 Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td>(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
ABT-267, ABT-450, ritonavir, and ribavirin</td><td rowspan="2"></td></tr>
<tr><td>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*)]
Ribavirin: 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide</td></tr>
<tr><td colspan="3">Title of Study: An Open-Label, Sequential Arm, Multicenter Study to Evaluate the Antiviral Activity, Safety and Pharmacokinetics of ABT-450 with Ritonavir (ABT-450/r) Dosed in Combination with ABT-267 With and Without Ribavirin (RBV) in Treatment-Naïve Subjects with Genotype 1, 2 or 3 Chronic Hepatitis C Virus (HCV) Infection</td></tr>
<tr><td colspan="3">Coordinating Investigator: Humberto Aguilar, MD, AGAF</td></tr>
<tr><td colspan="3">Study Sites: Fifteen investigative sites in the United States.</td></tr>
<tr><td colspan="3">Publications: 1 abstract</td></tr>
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Studied Period (Years):	**Phase of Development:** 2a
First Subject First Visit: 23 September 2011 Last Subject Last Visit: 31 May 2013	

Objectives:

The primary objective of this study was to assess the safety and antiviral activity (proportion of subjects with HCV RNA < lower limit of quantitation [LLOQ] at Week 4 and Week 12) of ABT-450/r administered in combination with ABT-267 with and without RBV under nonfasting conditions for 12 weeks in HCV genotype 1-, 2-, or 3-infected, treatment-naïve adults.

The secondary objectives of this study were to assess the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks post direct-acting antiviral therapy [DAA] therapy) or SVR_{24} (HCV RNA < LLOQ 24 weeks post DAA therapy); assess the percentage of subjects with HCV RNA < 1,000 IU/mL at Week 2; assess the percentage of subjects with HCV RNA < LLOQ at Week 4 of treatment; assess the time to failure to suppress or rebound in HCV RNA associated with this treatment regimen; assess the time to relapse after the end of the treatment regimen; assess the pharmacokinetics of ABT-450/r and ABT-267 with and without RBV in HCV-infected subjects; and assess the development and persistence of viral resistance with this treatment regimen.

Methodology:

This was a Phase 2a, multicenter, open-label, 2 sequential arm, combination treatment study that consisted of 2 phases, a treatment phase and a post-treatment phase. The treatment phase was designed to explore the antiviral activity, safety and pharmacokinetics of ABT-450/r dosed in combination with ABT-267 with and without RBV for up to 12 weeks. The post-treatment phase was designed to monitor and evaluate SVR_{12}, SVR_{24}, and the evolution and persistence of viral resistance to ABT-267 and ABT-450 in HCV genotype 1-, 2-, and 3-infected subjects who have been exposed to ABT-267 and ABT-450/r. Arms 1 and 2 were enrolled sequentially. Each arm contained 3 cohorts. The planned dosing schematic is shown below.

Arm	Cohort	Genotype	N	Treatment
1	I	1	10	ABT-450/r ≤ 200/100 mg QD and ABT-267 25 mg QD and RBV[a] 1,000 mg or 1,200 mg orally divided BID
	II	2	10	ABT-450/r ≤ 200/100 mg QD and ABT-267 25 mg QD and RBV[a] 1,000 mg or 1,200 mg orally divided BID
	III	3	10	ABT-450/r ≤ 200/100 mg QD and ABT-267 25 mg QD and RBV[a] 1,000 mg or 1,200 mg orally divided BID
2	IV	1	10	ABT-450/r ≤ 200/100 mg QD and ABT-267 25 mg QD
	V	2	10	ABT-450/r ≤ 200/100 mg QD and ABT-267 25 mg QD
	VI	3	10	ABT-450/r ≤ 200/100 mg QD and ABT-267 25 mg QD

BID = twice daily; QD = once daily

RBV was dosed at 1,000 mg (if body weight < 75 kg) or 1,200 mg (if body weight ≥ 75 kg) orally daily divided BID.

Number of Subjects (Planned and Analyzed):

Sixty subjects were planned (10 in each cohort). Sixty-one subjects (10 each in Cohorts I through V and 11 in Cohort VI) enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV-infected adults (18 to 65 years of age), with a body mass index ≥ 18 to < 35 kg/m^2. Females were either postmenopausal for at least 2 years, surgically sterile, or willing to use at least 2 effective forms of birth control. Males must have been surgically sterile or agreed to use at least 2 effective forms 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, 2, or 3 infection for at least 6 months, a plasma HCV RNA > 50,000 IU/mL, and FibroTest score ≤ 0.72 and aspartate aminotransferase (AST) to platelet ratio index ≤ 2, Fibroscan® result of < 9.6 kPa, or absence of cirrhosis based on a liver biopsy.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

	ABT-450	Ritonavir	ABT-267	RBV
Manufacturer	AbbVie/ Abbott	AbbVie/ Abbott	AbbVie/ Abbott	Generic Manufacturer
Mode of administration	Oral	Oral	Oral	Oral
Dosage form	Tablet	Soft gelatin capsule	Tablet	Tablet
Strength	50 mg	100 mg	25 mg	200 mg
Bulk lot number	11-000781	11-003407	10-004949 11-002033	11-002497

Duration of Treatment:

Study drugs (ABT-450/r, ABT-267 with or without RBV) were administered for up to 12 weeks.

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

Not applicable.

Criteria for Evaluation

Efficacy: The primary efficacy endpoint was the simple percentage of subjects with HCV RNA suppressed below the LLOQ from Week 4 through Week 12 (extended rapid virologic response [eRVR]) out of all subjects dosed. The secondary efficacy endpoints were: the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks post DAA therapy) or SVR_{24} (HCV RNA < LLOQ 24 weeks post-DAA therapy); the percentage of subjects with HCV RNA < 1,000 IU/mL at Week 2; the percentage of subjects with HCV RNA < LLOQ at Week 4; the time to virologic failure during treatment; and the time to relapse after treatment.

Resistance: The resistance endpoint was the frequency of mutations at each amino acid position by nucleotide sequencing compared with baseline and prototypic standard sequences.

Pharmacokinetics: Plasma concentrations for ABT-267, ABT-450, ritonavir, RBV, and possible metabolites of ABT-267 and ABT-450 were determined at each study visit up to 12 weeks.

Safety: Safety was evaluated based on adverse events, clinical laboratory determinations, vital signs, physical examination, and 12-lead electrocardiogram.

Statistical Methods

Efficacy:

For all efficacy endpoints, pairwise comparisons were made between Arm 1 and Arm 2 within each genotype (1, 2, or 3) and between arms across all genotypes combined.

For the primary endpoint (eRVR), a 95% binomial exact confidence interval (CI) for the percentage was supplied for each HCV genotype and overall, and the comparisons between Arm 1 and Arm 2 within each genotype (1, 2, or 3) and across arms with all genotypes combined were made using logistic regression with HCV subtype, baseline HCV RNA level, and interleukin 28B (IL28B) genotype as predictors, and a Cochran Mantel-Haenszel (CMH) mean score test adjusting for same variables (in case of separation of the logistic regression).

The percentage of subjects with HCV RNA < 1,000 IU/mL at Week 2, the percentage of subjects with HCV RNA < LLOQ at Week 4, and the percentage of subjects with SVR_{12} and SVR_{24} were presented with a 95% binomial exact CI and the same pairwise comparisons specified for the primary endpoint were made using the same models for logistic regression and CMH method as specified for the primary analyses.

The time to failure to suppress and rebound during treatment and the time to relapse after treatment were calculated using the Kaplan-Meier (product limit) method for right-censored observations. The time to rebound and the time to relapse were summarized with descriptive statistics (N, mean, median, and standard error) from the Kaplan-Meier method.

Resistance:

Amino acid changes for population sequencing were summarized by counting the number of subjects whose amino acid sequence did not match that of the baseline or prototypic standard at a codon for each visit, out of the total number of subjects with that baseline or prototypic standard amino acid at that codon. The amino acid changes for clonal sequencing were summarized for each subject by counting the number of clones whose sequencing data did not match those of the population baseline or prototypic standard at each visit and sequencing location, out of the total number of clones with those baseline or prototypic standard sequencing data.

The frequency of subjects with an emerged or enriched mutation from baseline was summarized by codon; a subject was considered to have emerged/enriched mutation if, at any time point after baseline, the increase from baseline in percentage of clones of any variants was greater than 20%. The emerged/enriched mutations at a codon in at least 2 subjects were summarized by HCV genotype, along with a listing of all these subjects and the emerged/enriched mutations. A listing of resistant variants at baseline was also provided.

Pharmacokinetics:

Pharmacokinetic parameters were not estimated. Plasma concentrations of ABT-267, ABT-450, ritonavir, and RBV that were collected prior to dosing were tabulated for each subject from Day 1 through Week 12 and at any time after the dose for each subsequent study visit. To generate a plasma concentration-time profile, samples were binned per sampling time postdose after Week 3. Summary statistics were computed for each sampling time and each bin.

Statistical Methods (Continued)

Safety:

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events were tabulated by primary System Organ Class and MedDRA preferred term by HCV genotype and overall within each arm and the specified pairwise comparison performed using Fisher's exact tests. Tabulations of treatment-emergent adverse events were also provided by severity rating and relationship to study drug.

Clinical laboratory tests were summarized at each visit by HCV genotype and overall within each arm. 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, and the specified pairwise differences analyzed using contrasts within an analysis of variance (ANOVA) model with HCV genotype and treatment arm as the factors. 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 who experienced postbaseline shifts in clinical laboratory values from low/normal to high and high/normal to low based on the normal range were summarized by HCV genotype and overall within each arm. In addition, the number and percentage of subjects with postbaseline values meeting prespecified criteria for potentially clinically significant (PCS) laboratory values were summarized by HCV genotype and overall within each arm. The prespecified pairwise comparisons were performed on the percentage of subjects with PCS laboratory values for each parameter using Fisher's exact tests.

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each postbaseline visit were summarized, and the specified pairwise differences analyzed using contrasts within an ANOVA model with HCV genotype and treatment arms as the factors. Frequencies and percentages of subjects with postbaseline values meeting predefined criteria for PCS vital sign values were summarized by HCV genotype and overall within each arm. The prespecified pairwise comparisons were performed on the percentage of subjects with PCS vital sign values for each parameter using Fisher's exact tests.

Summary/Conclusions

Efficacy Results:

ABT-267 and ABT-450/r with and without RBV were administered for 12 weeks in HCV genotype 1-, 2-, or 3-infected, treatment-naïve adults. HCV RNA levels were monitored through 48 weeks post-DAA treatment. Results for the primary efficacy endpoint, eRVR, showed that HCV RNA levels were maintained < LLOQ from Week 4 through Week 12 of treatment for 26/30 (86.7%) subjects in Arm 1 total (with RBV) and 19/31 (61.3%) subjects in Arm 2 total (without RBV). The difference was statistically significant ($P = 0.037$) and driven mainly by the difference in response among subjects with HCV genotype 3 (70.0% in Cohort III versus 18.2% in Cohort VI). For each genotype, a numerically greater percentage of subjects achieved the primary endpoint when ABT-450/r and ABT-267 were coadministered with RBV. The primary efficacy endpoint was also analyzed by HCV genotype and subtype, IL28B genotype, IL28B genotype category, race, ethnicity, sex, age, baseline HCV RNA level, baseline weight, and baseline HOMA-IR. Only HCV genotype showed a large difference in rates of eRVR across arms, and no subgroups showed a large difference in eRVR rates within a cohort. The majority of efficacy endpoints were statistically significantly different for Cohort III compared with Cohort VI (genotype 3 cohorts), which was the major reason for significant differences between Arm 1 total and Arm 2 total (with and without RBV, respectively).

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Secondary efficacy endpoint results were as follows:

- For each genotype, a numerically greater percentage of subjects achieved SVR_{12} when ABT-450/r and ABT-267 were administered with RBV compared with ABT-450/r and ABT-267 without RBV (Cohort I, 10/10 [100%] versus Cohort IV, 6/10 [60.0%]; Cohort II , 8/10 [80.0%] versus Cohort V, 6/10 [60.0%]; and Cohort III 5/10 [50.0%] versus Cohort VI, 1/11 [9.1%]). The percentage of subjects achieving SVR_{12} was statistically significantly greater for Cohort I compared with Cohort IV ($P = 0.037$), greater for Cohort III compared with Cohort VI ($P = 0.046$), and greater for Arm 1 total compared with Arm 2 total ($P = 0.005$).
- For each genotype, a numerically greater percentage of subjects achieved SVR_{24} when ABT-450/r and ABT-267 was administered with RBV compared with ABT-450/r and ABT-267 without RBV (Cohort 1, 10/10 [100%] versus Cohort IV, 6/10 [60.0%]; Cohort II, 8/10 [80.0%] versus Cohort V, 6/10 [60.0%]; and Cohort III 4/10 [40.0%] versus Cohort VI, 1/11 [9.1%]). The percentage of subjects achieving SVR_{24} was statistically significantly greater for Cohort I compared with Cohort IV ($P = 0.037$) and for Arm 1 total compared with Arm 2 total ($P = 0.014$). The only subject with SVR_{12} who did not have SVR_{24} (Subject 3207) was lost to follow-up after Post-Treatment Day 66, when he had undetectable HCV RNA.
- Of all the baseline characteristics examined in subgroup analyses of SVR_{12}, only HCV genotype showed large differences across the 2 arms, with Arm 2 (without RBV) being 20% to 41% lower than Arm 1, with the largest difference in genotype 3-infected subjects.
- All subjects had HCV RNA < 1,000 IU/mL at Week 2.
- At Week 4, HCV RNA levels were < LLOQ for 10/10 (100%) subjects in Cohort I, 10/10 (100%) subjects in Cohort II, 9/10 (90.0%) subjects in Cohort III, 10/10 (100%) subjects in Cohort IV, 9/10 (90.0%) subjects in Cohort V, and 3/11 (27.3%) subjects in Cohort VI. The percentage of subjects with HCV RNA < LLOQ at Week 4 was statistically significantly greater for Cohort III compared with Cohort VI ($P = 0.005$) and greater for Arm 1 total compared with Arm 2 total ($P = 0.004$).
- No subject failed to suppress. Rebound was experienced by 0/10 subjects in Cohort I, 1/10 (10.0%) subjects in Cohort II, 3/10 (30.0%) subjects in Cohort III, 1/10 (10.0%) subjects in Cohort IV, 1/10 (10.0%) subjects in Cohort V, and 8/11 (72.7%) subjects in Cohort VI. Relapse at any time was experienced by 2/7 subjects in Cohort III, 2/9 subjects in Cohort IV, 2/9 subjects in Cohort V, and 1/2 subjects in Cohort VI. All relapses occurred by the SVR_{12} window except for Subject [redacted] in Cohort VI who did not return for follow up between Post-Treatment Week 8 and Post-Treatment Week 36.

Summary/Conclusions (Continued)

Resistance Results:

Baseline analyses were conducted to determine the prevalence of resistance-associated variants and their impact on treatment outcome. Two of the 3 genotype 1a-infected subjects who did not achieve SVR_{12} had the pre-existing resistance-associated variants M28V or M28V + Q30H in NS5A.
One genotype 1a-infected subject who had Q30H/Q and Y93Y/H in NS5A and 1 genotype 2a-infected subject with T24A/T in NS5A at baseline both achieved SVR_{12}. Three genotype 3a-infected subjects had variants A166T or A166S in NS3 at baseline, and 2 of these subjects did not achieve SVR_{12}.

In the genotype 1a-infected subjects who did not achieve SVR_{12}, resistance-associated variants D168A, D168V, and Y56H + D168A were detected in NS3, and Q30R, V28V + Q30R, and V28V + H30H were detected in NS5A in samples closest in time after virologic failure. The NS3 variants remained detectable at Post-Treatment Week 24, but their prevalence was reduced to below the limit of detection (by clonal sequencing) by Post-Treatment Week 48. The NS5A variants seen at the time of virologic failure persisted to Post-Treatment Week 24 and/or 48. The NS3 variants D168A and D168V confer 50- to 100-fold resistance to ABT-450, while the double variant Y56H + D168A confers 352-fold resistance to ABT 450. The NS5A variant M28V + Q30H confers 47-fold resistance to ABT-267, whereas Q30R and M28V + Q30R confer at least 800-fold resistance to ABT-267.

In the genotype 2b-infected subjects who did not achieve SVR_{12}, resistance-associated variants D168A, D168V, and/or D168Y were detected in NS3, and L28F + M31 was detected in NS5A, in samples closest in time after virologic failure. The NS3 variant D168Y was detected in 1 subject at Post-Treatment Week 24, but the prevalence of all the NS3 variants was reduced to below the limit of detection (by clonal sequencing) by Post-Treatment Week 48. The NS5A variant L28F + M31 persisted to Post-Treatment Weeks 24 and 48. The NS3 variants D168A, D168V, and D168Y confer 49- to 78-fold resistance to ABT-450. The NS5A variant L28F in combination with M31 confers 247-fold resistance to ABT-267.

In the genotype 3a-infected subjects who did not achieve SVR_{12}, resistance associated variants Y56H, A166T, Q168H, Q168R, Y56H + A156G, Y56H + S166T, and/or Y56H + Q168R were detected in NS3 in samples closest in time after virologic failure. In NS5A, the predominant variant was Y93H, but 2 of the subjects also had M28T and L31F as minor variants. NS3 variants S166T and Q168H confer 3- to 6-fold resistance, A156G and Q168R confer 29- to 57-fold resistance, and Y56H + Q168R confers 170-fold resistance. NS5A variants M28T, L31F, and Y93H confer 659-, 28-, and 6,728-fold resistance to ABT-267, respectively. Only 2 subjects with NS3 variants A156G, A166T, and Q168L, and NS5A variant Y93H were available for follow up analysis. At Post-Treatment Weeks 24 and 48, A166T, but not A156G or Q168L, was detected in NS3 in both subjects, while Y93H in NS5A was still present in both subjects. One of the genotype 3a-infected subjects from Arm 1 (3271) had genotype 2b HCV at the time of virologic failure, indicating the likelihood of a new infection rather than relapse of the original infection.

Pharmacokinetic Results:

ABT-267, ABT-450, and ritonavir time-binned geometric mean C_{trough} values with or without RBV did not show any particular trend across all 3 genotypes. RBV concentrations also appeared comparable across all 3 genotypes.

Summary/Conclusions (Continued)

Safety Results:

In Arm 1, mean duration of DAA treatment ranged from approximately 78 days in Cohort III to 84 days in Cohorts I and II. In Arm 2, mean durations of DAA treatment were 84.0, 80.5, and 54.5 days in Cohorts IV, V, and VI, respectively.

One subject in Cohort IV died due to arteriosclerosis during the post-treatment phase and 2 additional subjects experienced nonfatal serious adverse events (1 subject each in Cohorts I and VI). None of these events were considered by the investigator to be related to the DAAs or RBV. One subject in Cohort VI prematurely discontinued study drug due to treatment-emergent adverse events of viral infection (nonserious) and meningitis herpes (serious) that were considered not related to study drug by the investigator.

The most common treatment-emergent adverse events in each arm were fatigue, nausea, headache, and diarrhea. The percentages of subjects that experienced adverse events of anemia, gastroesophageal reflux disease, nausea, fatigue, headache and depression events were at least 10.0% lower in Arm 2 (without RBV) than in Arm 1 (with RBV). The difference in adverse events between Arms 1 and 2 are not unexpected based upon the known tolerability profile of RBV. The majority of subjects had treatment-emergent adverse events that were at most mild or moderate in severity.

No adverse events identified by the narrow search for gallbladder-related disorders SMQ were observed. More subjects who received RBV (Arm 1) than who did not (Arm 2) experienced an adverse event identified by the drug-induced rash company MedDRA query search criteria. Since RBV is associated with rash and pruritus, this result is not unexpected. All of the rash events were mild in severity.

The mean decreases observed in hemoglobin and red blood cells in Arm 1 (subjects whose treatment regimen included RBV) at the end of treatment were up to 4-fold greater than those observed for Arm 2 (subjects whose treatment regimen did not include RBV), which is consistent with a known effect of RBV. However, no subject had a hemoglobin value that met the PCS criterion (< 80 g/L) during the study.

Mean decreases in alanine aminotransferase (ALT), AST, and gamma-glutamyl transferase of generally similar magnitude were observed across cohorts, and are indicative of viral clearance from the liver. Consistent with the known effect of ABT-450 + RBV on the bilirubin transporter organic anion transporting polypeptide 1B1, mean increases from baseline in total bilirubin, which were primarily due to the mean increases in indirect bilirubin, were observed in Arm 1. More subjects in Arm 1 versus Arm 2 had at least 1 PCS total bilirubin value that was more extreme than the baseline value (5 versus 1). Ribavirin is associated with hemolytic anemia, and the hyperbilirubinemia associated with RBV use is due to excess production of bilirubin due to red blood cell hemolysis. Consistent mean increases in alkaline phosphatase were observed in both arms at all time points during treatment; mean decreases from the Final Treatment Visit were observed post-treatment. No subject had an alkaline phosphatase value greater than grade 1. One subject in each arm had a transient ALT and/or AST value that met a PCS criterion and was at least grade 3. The elevated liver transaminases improved with continued dosing of the DAAs. No subject had liver function test values that met Hy's law (ALT or AST value ≥ 3× upper limit of normal [ULN] and total bilirubin value ≥ 2× ULN) or experienced a treatment-emergent adverse event that met the broad search criteria for drug-related hepatic disorders severe events standardized MedDRA query.

Conclusions:

A 12-week regimen of ABT-267 + ABT 450/r with or without RBV was well tolerated in HCV genotype 1-, 2-, or 3-infected, treatment-naïve adults. The primary endpoint (percentage of subjects with HCV RNA suppressed below the LLOQ from Week 4 through Week 12, eRVR) was achieved by 26/30 (86.7%) subjects in Arm 1 (with RBV) and 19/31 (61.3%) subjects in Arm 2 (without RBV). Overall, Arm 1 had higher SVR_{12} (76.7% versus 41.9%) and SVR_{24} (73.3% versus 41.9%) rates than Arm 2. These differences were driven mainly by the difference in response between arms among subjects with HCV genotype 3. These results support continued evaluation of ABT 450/r and ABT-267 with or without RBV for the treatment of chronic HCV genotype 1, 2, and 3 infection.