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-450, ritonavir, ABT-333, ribavirin</td><td rowspan="2"></td></tr>
<tr><td>Name of Active Ingredient:
ABT-450: (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate,
ritonavir: 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)</td></tr>
<tr><td colspan="3">Title of Study: An Open-Label Pilot Study to Evaluate the Antiviral Activity, Safety and Pharmacokinetics of ABT-450 with Ritonavir (ABT-450/r) Dosed in Combination with ABT-333 and Ribavirin (RBV) in Treatment-Naïve and Non-Responder Subjects with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection</td></tr>
<tr><td colspan="3">Coordinating Investigator: Fred Poordad, MD</td></tr>
<tr><td colspan="3">Study Sites: 11 investigative sites in the United States.</td></tr>
<tr><td colspan="3">Publications: Two abstracts and 1 manuscript</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 25 February 2011
Last Subject Last Visit: 19 October 2012</td><td>Phase of Development: 2a</td></tr>
</table>

Objectives:

The primary objective of this study was to assess the safety and antiviral activity (proportion of subjects with HCV RNA less than the lower limit of detection [LLOD] from Week 4 through Week 12) of ABT-450/r administered in combination with ABT-333 and RBV under nonfasting conditions for 12 weeks in HCV genotype 1 infected treatment-naïve adults and previous nonresponders to pegIFN/RBV treatment.

The secondary objectives of this study were: to assess the percentage of subjects with HCV RNA < 1,000 IU/mL at Week 2; to assess the percentage of subjects with HCV RNA < lower limit of quantitation (LLOQ) at Week 4 of treatment; to assess the time to failure to suppress or rebound in HCV RNA associated with these treatment regimens; to assess the time to relapse after the end of the treatment regimens; to assess the percentage of subjects with HCV RNA < LLOQ 12 weeks post direct-acting antiviral agent (DAA) therapy (SVR_{12}) or HCV RNA < LLOQ 24 weeks post DAA therapy (SVR_{24}); to assess the development and persistence of viral resistance with these treatment regimens; and to assess the pharmacokinetics of ABT-450/r and ABT-333 with RBV in HCV-infected subjects.

Methodology:

This was a Phase 2a multicenter, open-label, sequential, 3-arm, combination treatment study of a regimen of ABT-450/r, ABT-333, and RBV in HCV genotype 1-infected treatment-naïve adults and previous nonresponders to pegIFN/RBV treatment. At least 50% of the subjects enrolled in each arm were to be infected with genotype 1a HCV.

The study consisted of a treatment phase and post-treatment phase. The study included 2 treatment groups for treatment-naïve subjects and 1 treatment group for previous nonresponders. Enrollment of the 3 groups was sequential: Arm 1 subjects (treatment-naïve) were enrolled prior to assigning subjects to Arm 2 (treatment-naïve), and Arm 3 (nonresponders) enrolled following full enrollment of Arm 2. Ongoing review of safety data was planned to determine if subjects met the virologic stopping criteria. Enrollment in any arm could have been discontinued at any time by the medical monitor based on ongoing review of safety and antiviral activity.

Subjects who received at least 1 dose of DAA and who experienced virologic failure or relapse after therapy were eligible to receive pegIFN and RBV as nonprotocol treatment for up to 48 weeks. Pegylated interferon and RBV were to be started within 24 weeks of the end of DAA therapy and were only provided for subjects who were viremic. All subjects who received at least 1 dose of DAA were monitored for up to 48 weeks following the last DAA dose for viral resistance testing. Resistance monitoring was performed regardless of whether subjects received post-treatment pegIFN and RBV.

Number of Subjects (Planned and Analyzed):

Forty-five subjects (20 in Arm 1, 10 in Arm 2, and 15 in Arm 3) were planned. Fifty subjects (19 in Arm 1, 14 in Arm 2, and 17 in Arm 3) enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV-infected, treatment-naïve or previous nonresponders to pegIFN/RBV 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 practicing birth control. Male subjects and/or partner(s) had to be practicing at least 1 effective method of birth control. Subjects were in a condition of general good health, other than the HCV infection. Subjects had a chronic HCV genotype 1 infection for at least 6 months prior to study enrollment with no evidence of cirrhosis, bridging fibrosis, or liver pathology due to any cause other than chronic HCV infection.

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

	ABT-450	**Ritonavir**	**ABT-333**	**RBV**
Dose	250 mg or 150 mg QD	100 mg QD	400 mg BID	1,000 mg divided BID if body weight < 75 kg or 1,200 mg divided BID if body weight ≥ 75 kg
Mode of administration	Oral	Oral	Oral	Oral
Dosage form	Tablet	Soft gelatin capsule	Tablet	Tablet
Strength	50 mg	100 mg	400 mg	200 mg
Bulk lot number	10-003507	10-002930	10-000479 11-000511 11-000512	09-026055 10-003904

Duration of Treatment:

Study drug (ABT-450/r, ABT-333, + RBV) was 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 percentage of all dosed subjects with HCV RNA suppressed below the LLOD from Week 4 through Week 12. The secondary efficacy endpoints were: (1) the percentage of subjects with HCV RNA < 1,000 IU/mL at Week 2, (2) the percentage of subjects with HCV RNA less than the LLOQ at Week 4, (3) the percentage of subjects with SVR_{12} or SVR_{24}, (4) the time to virologic failure during treatment and (5) the time to relapse after treatment (confirmed HCV RNA > LLOQ). The resistance endpoints were (1) the fold change in half-maximal effective concentration (EC_{50}) levels at baseline compared with the prototypic standard, and at each postbaseline time point that was analyzed compared with baseline and prototypic standards and (2) the frequency of mutations at each amino acid position by nucleotide population sequencing at baseline compared with the prototypic standard sequence, and by nucleotide population and/or clonal sequencing for each postbaseline time point that was analyzed compared with baseline and prototypic standard sequences.

Criteria for Evaluation (Continued)

Pharmacokinetic:

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

Safety:

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

Statistical Methods

Efficacy:

For the primary endpoint, a 95% binomial exact confidence interval for the percentage in each treatment group was supplied, and the prespecified pairwise comparisons (Arm 1 versus Arm 2 and Arm 2 versus Arm 3) were made between the groups using logistic regression, with treatment group baseline HCV RNA level, IL28B genotype, and HCV subgenotype (1a or 1b) as predictors.

The percentages of subjects with HCV RNA < 1,000 IU/mL at Week 2, the percentage of subjects with HCV RNA < LLOD at Week 4, and the percentage of subjects with $SVR_{12actual}$ and $SVR_{24actual}$ were presented with 95% binomial exact confidence intervals for each treatment group, and the prespecified pairwise comparisons were made between the groups using logistic regression with treatment arm, baseline HCV RNA level, IL28B genotype, and HCV subgenotype (1a or 1b) as predictors.

The time to virologic failure 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 on-treatment virologic failure and the time to relapse were summarized with descriptive statistics (N, mean, median, and standard error) from the Kaplan-Meier method for each treatment group, and the prespecified pairwise comparisons were made between the group using log rank tests.

The resistance endpoints were (1) the fold change in EC_{50} levels at baseline compared with the prototypic standard, and at each postbaseline time point that was analyzed compared with baseline and prototypic standards and (2) the frequency of mutations at each amino acid position by nucleotide population sequencing at baseline compared with the prototypic standard sequence, and by nucleotide population and/or clonal sequencing for each postbaseline time point that was analyzed compared with baseline and prototypic standard sequences.

Pharmacokinetic:

Plasma concentrations for ABT-333, ABT-450, RBV, and ritonavir and the M1 metabolite of ABT-333 were determined at each study visit up to 12 weeks. Summary statistics were computed for each sampling time. To generate a plasma concentration-time profile, samples were binned per sampling time postdose beginning with Week 3. Summary statistics were computed for each bin.

Safety:

Adverse events were coded using Medical Dictionary for Regulatory Activities (version 15.0). The number and percentage of subjects in each treatment group with treatment-emergent adverse events were tabulated by primary System Organ Class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Tabulations were also provided by severity rating and relationship to study drug.

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 central laboratory used in this study. The number and percentage of subjects in each treatment group 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. In addition, the number and percentage of subjects in each treatment group with postbaseline values meeting prespecified criteria for potentially clinically significant laboratory values were summarized.

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each postbaseline visit were summarized descriptively for each treatment group. Frequencies and percentages of subjects in each treatment group with postbaseline values meeting predefined criteria for potentially clinically significant vital signs values were summarized.

Summary/Conclusions

Efficacy Results:

ABT-450/r, ABT-333, and RBV were administered for 12 weeks (Day 1 to Week 12; DAA treatment) to subjects who were treatment-naïve and subjects who were previous nonresponders to pegIFN/RBV treatment. HCV RNA levels were monitored through 48 weeks post-DAA treatment. Results for the primary efficacy endpoint showed that HCV RNA levels were maintained < LLOD from Week 4 through Week 12 of treatment for 17/19 (89.5%) subjects in Arm 1, 11/14 (78.6%) subjects in Arm 2, and 10/17 (58.8%) subjects in Arm 3. The primary efficacy endpoint was also analyzed by HCV genotype and subtype, race, ethnicity, gender, age, weight, baseline HCV RNA level, baseline median HCV RNA level, and baseline HOMA-IR. Although sample sizes were small, the majority of subjects within each arm maintained HCV RNA < LLOD from Week 4 through Week 12 for most of these subgroups. No efficacy endpoint was statistically significantly different for ABT-450 dosed at 250 mg QD (Arm 1) compared with ABT-450 dosed at 150 mg QD (Arm 2).

Secondary efficacy endpoint results were as follows:

- At Week 2, HCV RNA levels were < 1,000 IU/mL for 19/19 (100%) subjects in Arm 1, 13/14 (92.9%) subjects in Arm 2, and 17/17 (100%) subjects in Arm 3.
- At Week 4, HCV RNA levels were < LLOQ for 19/19 (100%) subjects in Arm 1, 13/14 (92.9%) subjects in Arm 2, and 15/17 (88.2%) subjects in Arm 3.
- $SVR_{12actual}$ was achieved by 18/19 (94.7%) subjects in Arm 1, 13/14 (92.9%) subjects in Arm 2, and 8/17 (47.1%) subjects in Arm 3. The percentage of subjects achieving $SVR_{12actual}$ was statistically significantly greater for Arm 2 compared with Arm 3 ($P = 0.012$).
- $SVR_{24actual}$ was achieved by 18/19 (94.7%) subjects in Arm 1, 12/14 (85.7%) subjects in Arm 2, and 8/17 (47.1%) subjects in Arm 3. The percentage of subjects achieving $SVR_{24actual}$ was statistically significantly greater for Arm 2 compared with Arm 3 ($P = 0.012$).
- No confirmed rebounds or relapses occurred for subjects completing treatment in Arm 1 or Arm 2.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

- Rebound or failure to suppress occurred 7/17 (41.2%) subjects in Arm 3 (1 subject did not truly rebound but had a spurious HCV RNA level of 27 IU/mL at Week 6), with a mean time to rebound or failure to suppress of 62.6 days.
- After completing the treatment as assigned, relapse occurred for 3/11 (27.3%) subjects in Arm 3, with a mean time to relapse of 15.8 days.

The efficacy of ABT-450/r + ABT-333 + RBV in treatment-naïve subjects was comparable by all endpoints studied for ABT-450/r doses of 250/100 mg or 150/100 mg, with 94.7% and 92.9%, respectively, achieving $SVR_{12actual}$. Subgroup analyses did not demonstrate any impact on efficacy. In contrast, the proportions of subjects achieving $SVR_{12actual}$ or $SVR_{24actual}$ were significantly greater among treatment-naïve subjects than among prior pegIFN/RBV nonresponders, with 47.1% of nonresponders achieving $SVR_{12actual}$.

One of the secondary objectives was to assess the development and persistence of viral resistance with the treatment regimens. Nine of 17 prior pegIFN/RBV nonresponders experienced virologic failure in this study, 8 infected with HCV genotype 1a and 1 with genotype 1b. At baseline, none of the genotype 1a-infected virologic failure subjects had resistance-associated variants in either NS3 or NS5B; however, the single genotype 1b-infected subject who experienced virologic failure had multiple resistance-associated variants present at baseline in NS3. At the time of virologic failure, samples from 7/8 subjects infected with genotype 1a and 1 of 1 subject infected with genotype 1b had detectable resistance-associated variants, and all of the virologic failure samples that contained resistance-associated variants also exhibited phenotypic resistance to ABT-450 and ABT-333. The most prevalent treatment emerged resistance-associated variant in NS3 was D168V, with other variants at D168 (A, E, K, or Y) seen less frequently. One subject had R155K at failure. In NS5B, resistant variants emerged at amino acid residues 316, 414, 554, 556, and/or 559, with S556G being seen most frequently. By Post-Treatment Week 48, resistance-associated variants were no longer detectable in either NS3 or NS5B in available samples from 3 of 5 subjects who experienced virologic failure.

Pharmacokinetic Results:

ABT-450 exposures increased in a supraproportional manner with an increase in ABT-450 dose from 150 mg to 250 mg, consistent with earlier findings. Ritonavir, ABT-333, the M1 metabolite of ABT-333, and RBV concentrations were comparable among Arms 2 and 3 (ABT-450 150 mg) and Arm 1 (ABT-450 250 mg).

Pharmacodynamic Results:

There was no correlation between the viral response and the ABT-450, ABT-333, and RBV exposures as average concentrations.

Summary/Conclusions (Continued)

Safety Results:

The majority of subjects were compliant with all 4 study drugs for the duration of the 12 week DAA treatment period, with a mean (range) treatment duration of 78.4 (13 to 86) days. No deaths or serious adverse events were reported during the study.

Forty-three (86%) subjects experienced at least 1 treatment-emergent adverse event. Treatment-emergent adverse events experienced by at least 25% of subjects in any arm included fatigue, headache, insomnia, and dizziness. The majority of adverse events were mild, and only 1 subject discontinued study drug due to a treatment-emergent adverse event (events of alanine aminotransferase increased and aspartate aminotransferase increased that were considered possibly related to DAAs). Ten subjects across the 3 treatment arms experienced treatment-emergent adverse events that met the drug-induced rash company MedDRA query search criteria, most of which were rash and pruritus. The majority of these events were mild in severity, and there were no severe cutaneous reactions reported. All events resolved either while DAA therapy was ongoing or following completion of DAA therapy. Since all subjects received RBV, and RBV is associated with rash and pruritus, it is difficult to attribute these events with certainty to the DAAs.

Mean decreases in hemoglobin of approximately 20 g/L were observed in each treatment arm (each of which included RBV) at the end of DAA treatment, which is consistent with the known effect of RBV. However, no hematology value met a PCS criterion during the study. No other consistent hematologic laboratory abnormalities were observed.

ABT-450 is a known inhibitor of the organic anion transporting polypeptide 1B1 bilirubin transporter, and increases in total bilirubin (predominantly indirect bilirubin) have been observed with ABT-450 administration. Transient elevations of total and indirect bilirubin during DAA treatment were observed in approximately half of subjects in all 3 treatment arms, with total bilirubin levels reaching $\geq 2 \times$ ULN in 6 subjects. These PCS bilirubin elevations were largely due to indirect bilirubin, and none of these subjects had associated elevations of ALT or AST.

Conclusions:

A 12-week regimen of ABT 450/r and ABT 333 with RBV was well tolerated in subjects who were treatment-naïve and subjects who were previous nonresponders to pegIFN/RBV treatment. The primary endpoint (HCV RNA levels < LLOD from Week 4 through Week 12 of treatment) was achieved for 17/19 (89.5%) subjects in Arm 1, 11/14 (78.6%) subjects in Arm 2, and 10/17 (58.8%) subjects in Arm 3. $SVR_{12actual}$ was achieved by 18/19 (94.7%) subjects in Arm 1, 13/14 (92.9%) subjects in Arm 2, and 8/17 (47.1%) subjects in Arm 3. The results of this study justify continued evaluation of pegIFN-free combination DAA regimens in patients with HCV genotype 1 infection, with an ABT-450/r dose of 150/100 mg.

Date of Report: 17Jul2013