

## 2.0 Synopsis

<b>AbbVie Inc.</b>	<b>Individual Study Table Referring to Part of Dossier:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> ABT-267, ABT-450, ritonavir, ABT-333, ribavirin	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> ABT-267: Dimethyl ((2 <i>S</i> ,5 <i>S</i> )-1-(4- <i>tert</i> -butylphenyl) pyrrolidine-2,5-diyl)bis{ benzene-4,1-diylcarbamoyl(2 <i>S</i> )pyrrolidine-2,1-diyl[(2 <i>S</i> )-3-methyl-1-oxobutane-1,2-diyl]}biscarbamate hydrate ABT-450: (2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i> )- <i>N</i> -(cyclopropylsulfonyl)-6- {[5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2- <i>a</i> ][1,4]diazacyclopentadecine-14 <i>a</i> (5 <i>H</i> )-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, [5 <i>S</i> -(5 <i>R</i> *,8 <i>R</i> *,10 <i>R</i> *,11 <i>R</i> *)] ABT-333: (sodium <i>N</i> -{6-[3- <i>tert</i> -butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2 <i>H</i> )-yl)-2-methoxyphenyl]naphthalen-2-yl}methanesulfonamide) Ribavirin: 1-β-D-ribofuranosyl-1 <i>H</i> -1,2,4-triazole-3-carboxamide	<b>Page:</b>	
<b>Title of Study:</b> An Open-Label, Multiple Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of ABT-267 in HCV Infected Subjects		
<b>Investigator:</b> Franco A. Felizarta, MD		
<b>Study Site(s):</b> 4 investigative sites in the United States		
<b>Publications:</b> 1 abstract		

<p><b>Studied Period (Years):</b> First Subject First Visit: 08 February 2012 Last Subject Last Visit: 13 June 2013</p>	<p><b>Phase of Development: 2</b></p>
<p><b>Objective(s):</b> The primary objective of this study was to assess the safety, tolerability, and antiviral activity (maximal decrease from baseline in log<sub>10</sub>IU/mL hepatitis C virus [HCV] RNA levels) of multiple ascending doses of ABT-267 administered as monotherapy under nonfasting conditions in treatment-naïve HCV genotype 1-infected adults. The secondary objectives of this study were to assess the safety, tolerability, and antiviral activity of combination therapy with ABT-267, ABT-450/r, ABT-333, and ribavirin (RBV); to assess the pharmacokinetics of ABT-267 during monotherapy and of ABT-267, ABT-450/r, ABT-333, and RBV during combination therapy; and to explore the relationship between ABT-267 exposure and viral load response following multiple doses of ABT-267 during monotherapy.</p>	
<p><b>Methodology:</b> This was a Phase 2, multicenter, open-label study to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of ABT-267 as 2-day monotherapy followed by ABT-267 coadministered with ABT-450/r, ABT-333, and RBV for 12 weeks in treatment-naïve, HCV genotype 1-infected subjects. This study consisted of 3 periods: a 2-day ABT-267 Monotherapy Treatment (MT) Period, a 12-week (84 days) Combination Treatment (CT) Period, and a 48-week Post-Treatment (PT) Period for evaluation of sustained virologic response (SVR) and resistance monitoring. Total treatment duration was 86 days. Screening evaluations were to be completed within 42 days of the first dose of study drug. Subjects were to receive doses of ABT-267 from 1.5 mg up to 50 mg daily on MT Period Days 1 and 2. The trial only enrolled 2 of the planned arms with doses of 1.5 mg or 25 mg daily. Subjects completing the ABT-267 MT Period proceeded to the CT Period (CT Period Day 1/Day 3 through CT Period Week 12/Day 86), during which HCV treatment was expanded to include the coadministration of ABT-267, ABT-450/r, ABT-333, and RBV. All study drugs were administered once daily (QD) during the CT Period, except for ABT-333 and RBV, which were dosed twice daily (BID). All subjects who received at least 1 dose of direct-acting antiviral agent (DAA) were to enter the PT Period and were to be monitored for antiviral activity and virologic resistance on an outpatient basis for an additional 48 weeks following the last dose of DAA.</p>	
<p><b>Number of Subjects (Planned and Analyzed):</b> Up to 24 subjects were planned. Twelve subjects (6 in Arm 1 and 6 in Arm 2) were enrolled and received at least 1 dose of study drug.</p>	
<p><b>Diagnosis and Main Criteria for Inclusion:</b> Subjects were HCV-infected adults (18 to 70 years of age, inclusive), with a body mass index <math>\geq 18</math> to <math>&lt; 38</math> kg/m<sup>2</sup>. Females were either postmenopausal for at least 2 years, surgically sterile, or of childbearing potential and practicing 2 effective forms of birth control. 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 <math>&gt; 10,000</math> IU/mL, and FibroTest<sup>®</sup> score <math>\leq 0.72</math> and aspartate aminotransferase (AST) to platelet ratio index <math>\leq 2</math> or FibroScan<sup>®</sup> result <math>&lt; 9.6</math> kPa or absence of cirrhosis and extensive bridging based on a liver biopsy.</p>	

<b>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</b>					
	<b>ABT-267</b>	<b>ABT-333</b>	<b>ABT-450</b>	<b>Ritonavir</b>	<b>RBV</b>
Manufacturer	AbbVie/ Abbott	AbbVie/ Abbott	AbbVie/ Abbott	AbbVie/ Abbott	Generic Manufacturer Three Rivers Pharmaceuticals, Inc.
Mode of administration	Oral	Oral	Oral	Oral	Oral
Dosage form	Tablet	Tablet	Tablet	Soft Gelatin Capsule	Tablet
Strength	1.5, 5, and 25 mg	400 mg	50 mg	100 mg	200 mg
Bulk Lot Number	1.5 mg: 10-002626 5 mg: 10-004948 25 mg: 11-002034	11-002720	11-000781	11-005635	11-002516
<b>Duration of Treatment:</b>					
ABT-267 was administered for 2 days during the MT Period followed by administration of ABT-267, ABT-450/r, ABT-333, and RBV for 12 weeks during the CT Period.					
<b>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</b>					
Not applicable.					
<b>Criteria for Evaluation</b>					
<b>Efficacy:</b>					
The primary efficacy endpoint was the maximal decrease from baseline in log <sub>10</sub> HCV RNA levels during ABT-267 MT Period (through prior to first dose of combination DAA on CT Period Day 1). Secondary efficacy endpoints were: (1) the percentage of subjects with SVR 12 weeks postdosing (SVR <sub>12</sub> ) and the percentage of subjects with SVR 24 weeks post-dosing (SVR <sub>24</sub> ), (2) the percentage of subjects with rapid virologic response (RVR) (HCV RNA < lower limit of quantitation [LLOQ] at CT Period Week 4), (3) the percentage of subjects with complete early virologic response (cEVR) (HCV RNA < LLOQ at CT Period Week 12), (4) the percentage of subjects with extended RVR (eRVR) (an HCV RNA < LLOQ at CT Period Week 4 through CT Period Week 12), and (5) the exposure-response relationship between ABT-267 concentrations and antiviral efficacy was explored.					

**Criteria for Evaluation (continued)**

**Resistance:**

The resistance endpoints were: (1) the fold change from baseline and reference HCV samples in the half maximal effective concentration ( $EC_{50}$ ) at various time points, (2) the identification of mutations at each amino acid position by population and/or clonal nucleotide sequencing compared with baseline and prototypic sequences, and (3) development and persistence of viral resistance with these treatment regimens.

**Pharmacokinetic:**

Plasma concentrations of study drugs and their metabolites were determined.

**Safety:**

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

**Statistical Methods**

**Efficacy:**

For each treatment arm, the primary efficacy endpoint was summarized descriptively using N, mean, median, standard deviation (SD), minimum and maximum. The maximum  $\log_{10}$  changes in HCV RNA level were compared between the ABT-267 1.5 mg and 25 mg arms using an analysis of covariance with the baseline  $\log_{10}$  HCV RNA values as a covariate and with an effect for treatment arm.

The percentages of subjects with RVR, cEVR, eRVR, SVR<sub>12</sub>, and SVR<sub>24</sub> and the corresponding 95% exact confidence interval (CI) were calculated for each treatment arm.

The percentages of subjects with SVR 12 weeks after the last planned dose of DAA combination therapy (SVR<sub>12planned</sub>), SVR 24 weeks after the last planned dose of DAA combination therapy (SVR<sub>24planned</sub>), and undetectable/unquantifiable at each visit and the corresponding 95% exact CIs were calculated for each treatment arm. Similarly, the percentage of subjects who failed to suppress or who rebounded and the percentage of subjects who relapsed were calculated for each treatment arm along with the corresponding 95% exact CIs.

From HCV RNA levels, the time to suppression during treatment was calculated for each subject, and the median time and 95% CI were estimated for each treatment arm using Kaplan-Meier methodology, where appropriate.

Summary statistics for the time to suppression after treatment were generated using right-censored observations; thus, subjects who prematurely discontinued were included to the point at which they no longer had results.

The mean change from baseline in HCV RNA to each time point was calculated for each treatment arm. Missing values were not imputed for analyses of change from baseline in HCV RNA.

**Resistance:**

The fold changes at each time point were summarized with mean, standard error, median, minimum, and maximum.

**Statistical Methods (continued)**

**Resistance (continued):**

Among those with population sequencing performed, the amino acid changes in each treatment arm in mixed population sequencing were to be 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 for whom clonal sequencing was performed by counting the number of clones whose sequencing data did not match that of the population baseline or prototypic standard at each visit and sequencing location, out of the total number of clones with that baseline or prototypic standard sequencing data. Signature mutations were identified by AbbVie Virology, and amino acid changes for population and clonal sequencing were summarized for these signature mutations.

The frequency of subjects in each treatment arm with an emerged or enriched mutation from baseline was summarized by codon; a subject was to be considered to have an emerged/enriched mutation if, at any time point with clonal sequencing performed after baseline, the increase from baseline in percentage of clones of any variants was  $\geq 20\%$ . The emerged/enriched mutations at a codon in at least 2 subjects were summarized, along with a listing of all these subjects and the emerged/enriched mutations.

**Pharmacokinetic:**

The maximum plasma concentration ( $C_{max}$ ), area under the curve from time zero to 24 hours ( $AUC_{24}$ ), and trough concentration after first dose (i.e., predose concentration on Day 2) were determined using noncompartmental analyses and summarized after the first dose of ABT-267 on MT Period Day 1.

Plasma concentrations of study drugs and their metabolites were tabulated for each subject and arm.

**Safety:**

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) (Version 16.0). The number and percentage of subjects with treatment-emergent adverse events were tabulated by primary System Organ Class and MedDRA preferred term. Tabulations were also provided by severity rating and relationship to study drug.

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. 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 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 with postbaseline values meeting prespecified criteria for potentially clinically significant (PCS) laboratory values were summarized. The frequency and percentage of subjects with a maximum Common Terminology Criteria for Adverse Events grade of 1, 2, 3, or 4 were summarized for hemoglobin, absolute neutrophil count, and the liver function tests of alanine aminotransferase (ALT), AST, alkaline phosphatase, and total bilirubin.

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

## Summary/Conclusions

### Efficacy Results:

Results for the primary efficacy endpoint showed that the maximal decrease from baseline in HCV RNA during ABT-267 monotherapy was  $-1.6 \log_{10}$  IU/mL for Arm 1 and  $-3.1 \log_{10}$  IU/mL for Arm 2. The difference between the 2 arms was statistically significant ( $P = 0.035$ ). Analysis of the primary efficacy endpoint was also performed using the following subgroups: HCV genotype, baseline HCV RNA level, interleukin 28B genotype, and baseline interferon gamma-induced protein 10. For the majority of subgroups, the maximal decrease was greater in Arm 2 than in Arm 1. Subjects infected with HCV genotype 1a who received ABT-267 25 mg QD (Arm 2) experienced a greater decrease in HCV RNA compared to those who received ABT-267 1.5 mg QD (Arm 1). Maximum decrease in HCV RNA from baseline was similar across arms among genotype 1b-infected subjects. These data support the selection of the 25 mg dose of ABT-267 to be used in combination with other DAAs for the treatment of chronic HCV infection.

Results for secondary endpoints and additional endpoints were generally similar for Arm 1 and Arm 2. Secondary efficacy endpoint results were as follows:

- RVR was achieved by 5/6 (83.3%) subjects in Arm 1 and 6/6 (100%) subjects in Arm 2;
- end-of-treatment response was achieved by 5/6 (83.3%) subjects in each arm;
- SVR<sub>12</sub> and SVR<sub>24</sub> were both achieved by 5/6 (83.3%) subjects in each arm;
- eRVR (HCV RNA < LLOQ at CT Week 4 through CT Week 12) was achieved by 5/6 (83.3%) subjects in each arm.

One subject in each treatment arm prematurely discontinued the study during the Treatment Period without on-treatment virologic failure.

The high proportion of subjects achieving SVR<sub>12</sub> and SVR<sub>24</sub> following 12 weeks of ABT-450/r, ABT-267, and ABT-333 coadministered with RBV without interferon supports the continued development of this regimen for the treatment of chronic HCV infection.

**Summary/Conclusions (Continued)**

**Resistance Results:**

The presence of pre-existing resistance-associated variants in nonstructural protein 3 (NS3)/nonstructural protein 4A (NS4A), nonstructural protein 5A (NS5A), and non-nucleoside non-structural protein 5B (NS5B) was analyzed from baseline samples for all 12 subjects. Resistance-associated variants were not detected in NS3/4A. One genotype 1a-infected subject who achieved SVR<sub>12</sub> had C451Y in NS5B. Although other variants at amino acid position 451 confer resistance to ABT-333, it is not known if C451Y is a resistance-associated variant. One genotype 1a-infected subject had the double variant Q30H + Y93H in NS5A at Day 1, and this sample conferred 2548-fold resistance to ABT-267. There was no HCV RNA reduction in this subject during the ABT-267 monotherapy period; however, this subject achieved SVR<sub>12</sub> after receiving the 3-DAA + RBV regimen.

On Day 3 of ABT-267 monotherapy, 6/6 subjects in the 1.5 mg treatment arm, and 2/6 subjects in the 25-mg treatment arm had HCV RNA  $\geq$  1,000 IU/mL, allowing for resistance analyses to be conducted. In the 25-mg treatment arm, samples from both subjects that had sufficient titer for analysis had resistance-associated variants in > 98% of clones. Five of the 6 subjects receiving 1.5 mg monotherapy had resistance-associated variants present at Day 3, although in a lower percentage of clones than was seen in the samples from subjects dosed with 25 mg ABT-267, perhaps as a result of lower drug pressure at the lower ABT-267 dose. These data support the hypothesis that the use of the higher ABT-267 dose for the treatment of chronic HCV infection may minimize the percentage of patients who experience the enrichment of certain NS5A variants, such as M28V in genotype 1a.

In genotype 1a, the predominant resistance-associated variants that were observed in subjects on Day 3 of treatment with ABT-267 were M28T, M28V, Q30R, Y93C, and Y93H. The M28V variant confers 58-fold resistance to ABT-267 in the genotype 1a-H77 replicon, whereas all other variants confer more than 800-fold resistance to ABT-267. Y93H was the predominant variant detected in both the genotype 1b-infected subjects, and the Y93H variant in genotype 1b-Con replicon confers 77-fold resistance to ABT-267.

**Pharmacokinetic Results:**

Dose-normalized ABT-267 C<sub>max</sub> and AUC<sub>24</sub> for the hot-melt extrusion (HME) tablet were 48% and 56% higher, respectively, than the spray-dried dispersion (SDD) tablet. [REDACTED]

[REDACTED]

### **Safety Results:**

In general, ABT-267 was well tolerated when administered as monotherapy or in combination with ABT-450/r, ABT-333, and RBV. Treatment-emergent adverse events across both arms were mostly mild and considered unrelated to DAA by the investigator. While more adverse events were reported in Arm 2 than Arm 1, the adverse events reported in this study are consistent with those seen in previous studies of ABT-267 and ABT-450/r coadministered with ABT-333 and RBV in HCV genotype 1-infected subjects. No new safety signals were identified.

Two subjects in Arm 2 experienced treatment-emergent serious adverse events (labyrinthitis and mania). Neither event was considered by the investigator or AbbVie to be related to the DAAs or RBV. The event of mania led to premature discontinuation of study drug.

Three subjects in Arm 2 experienced a treatment-emergent adverse event that met the drug-induced rash company MedDRA query search criteria (dermatitis in 1 subject and rash in 2 subjects). All 3 rash adverse events were considered mild in severity by the investigator.

Mean decreases that were of similar magnitude in each arm were observed in hemoglobin and red blood cell (RBC), which are consistent with known effects of RBV. However, no subject had a hemoglobin value that met the PCS criterion during the study. Mean increases from the Final Treatment Visit to PT Week 4 in hemoglobin and RBC were observed in each arm.

Mean decreases in ALT, AST, and gamma-glutamyl transferase were observed in each arm, and are indicative of viral clearance from the liver. Hyperbilirubinemia is known to occur with RBV as a result of red cell hemolysis and excess production of bilirubin. In addition, 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. Mean increases from baseline in total and indirect bilirubin were observed in each arm at the Final Treatment Visit, with the mean increase greater in Arm 2 compared with Arm 1. At PT Week 4, mean decreases from baseline were observed in total bilirubin, direct bilirubin, and indirect bilirubin. One subject in Arm 1 and 2 subjects in Arm 2 had at least 1 PCS total bilirubin value that was more extreme than the baseline value; one of these subjects (Arm 2) had a post-nadir value that reached grade 3. No subjects had an ALT, AST, or alkaline phosphatase value that was grade 3 or 4 or that met a PCS criterion, or had laboratory values that met the criteria for Hy's law (ALT or AST value  $\geq 3 \times$  upper limit of normal [ULN] and total bilirubin value  $\geq 2 \times$  ULN).

### **Conclusions:**

Two days of ABT-267 monotherapy followed by a 12-week regimen of ABT-267 (1.5 mg QD in Arm 1, 25 mg QD in Arm 2) + ABT-450/r + ABT-333 + RBV was well tolerated in HCV genotype 1-infected, treatment-naïve adults. The primary endpoint (maximal decrease from baseline in  $\log_{10}$  HCV RNA levels during monotherapy) was  $-1.6 \log_{10}$  IU/mL and  $-3.1 \log_{10}$  IU/mL in Arms 1 and 2, respectively ( $P = 0.035$ ). The percentage of subjects achieving SVR<sub>12</sub> was 83.3% in each arm. Exposure-response analysis indicates that 25 mg is the optimal dose for maximum viral load decline in genotype 1-infected subjects following monotherapy with ABT-267. The results of this study justify continued evaluation of combination DAA regimens in patients with HCV genotype 1 infection.

**Date of Report:** 10Oct2013