

## 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, pegylated interferon, and 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	<b>Page:</b>	
<b>Title of Study:</b> A Blinded, Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety, Pharmacokinetics, and Antiviral Activity of ABT-267 in Combination with Peginterferon $\alpha$ -2a and Ribavirin (pegIFN/RBV) in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection		
<b>Coordinating Investigator:</b> Thomas Marbury, MD		
<b>Study Sites:</b> 9 investigative sites in the United States and Puerto Rico.		
<b>Publications:</b> Two abstracts		
<b>Studied Period (Years):</b> First Subject First Visit: 18 March 2011 Last Subject Last Visit: 15 February 2013	<b>Phase of Development:</b> 2a	
<p><b>Objectives:</b></p> <p>The primary objective of this study was to compare the safety, pharmacokinetics, and 4-week rapid virologic response (RVR) (percentage of subjects with hepatitis C virus (HCV) RNA &lt; lower limit of detection [LLOD] at Week 4) of 3 different doses of ABT-267 in combination with pegylated interferon (pegIFN)/ribavirin (RBV) compared with pegIFN/RBV alone (ABT-267 placebo), administered under nonfasting conditions for 12 weeks in HCV genotype 1-infected, treatment-naïve adults.</p> <p>The secondary objectives of this study were to evaluate and compare the following endpoints between the ABT-267 with pegIFN/RBV treatment groups and the pegIFN/RBV alone treatment group: the percentage of subjects with partial early virologic response (pEVR) (HCV RNA decrease &gt; 2 log<sub>10</sub> IU/mL at Week 12) and the percentage of subjects with complete early virologic response (cEVR) (HCV RNA &lt; LLOD at Week 12); the percentage of subjects with sustained virologic response (SVR) 12 weeks post-pegIFN/RBV dosing (SVR<sub>12</sub>) and the percentage of subjects with SVR 24 weeks post-pegIFN/RBV dosing (SVR<sub>24</sub>); the time to suppression (HCV RNA &lt; LLOD); the exposure-response relationship between ABT-267 concentrations and antiviral efficacy; and the percentage of subjects with extended rapid virologic response (eRVR) (HCV RNA &lt; LLOD at Week 4 through Week 12).</p>		

**Methodology:**

This was a Phase 2a, blinded, randomized, placebo-controlled, dose-ranging study, enrolling up to 39 chronically HCV genotype 1-infected, treatment-naïve subjects. The study consisted of 2 substudies. Substudy 1 was the ABT-267 or placebo + pegIFN/RBV Treatment Phase, and Substudy 2 was the Post ABT-267 or Placebo Treatment Phase.

Substudy 1 was designed to assess the antiviral activity, safety, and pharmacokinetics of ABT-267 dosed at 5 mg once daily (QD), 50 mg QD, or 200 mg QD or placebo in combination with pegIFN/RBV. Subjects who completed or prematurely discontinued Substudy 1 were to have Week 12/premature discontinuation procedures performed and enter Substudy 2 the next day.

Substudy 2 was designed to continue administration of pegIFN/RBV alone for an additional 36 weeks to a total of 48 weeks of pegIFN/RBV for each subject. In addition, all subjects who received at least 1 dose of ABT-267 or placebo in Substudy 1 were to be monitored for viral resistance on an outpatient basis for 48 weeks following the last dose of ABT-267 or placebo, regardless of whether they prematurely discontinued or completed Substudy 1 as planned, and regardless of whether or not they discontinued pegIFN/RBV in Substudy 2. Finally, all subjects were followed for 24 weeks post-pegIFN/RBV treatment in Substudy 2 to obtain SVR<sub>12</sub> and SVR<sub>24</sub> data.

**Number of Subjects (Planned and Analyzed):**

Thirty-nine subjects were planned (9 placebo subjects and 10 ABT-267 subjects in each dose group [5, 50, and 200 mg]). Thirty-seven subjects (9 placebo, 9 ABT-267 5 mg, 9 ABT-267 50 mg, and 10 ABT-267 200 mg) 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  $\geq 18$  to  $< 35$  kg/m<sup>2</sup>. Females were either postmenopausal for at least 2 years or surgically sterile. Males must have been surgically sterile or agreed to practice at least 1 effective method 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  $> 50,000$  IU/mL, and Fibro Test score  $\leq 0.72$  and aspartate aminotransferase to platelet ratio index  $\leq 2$  or absence of cirrhosis based on a liver biopsy.

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

Investigational Product	ABT-267		Placebo for ABT-267		Ribasphere <sup>®</sup> RBV	Pegasys <sup>®</sup> pegIFN $\alpha$ -2a
Manufacturer	AbbVie/ Abbott	AbbVie/ Abbott	AbbVie/ Abbott	AbbVie/ Abbott	Three Rivers Pharmaceuticals, Inc.	Roche
Mode of administration	Oral	Oral	Oral	Oral	Oral	SC injection
Dosage form	Tablet	Tablet	Tablet	Tablet	Tablet	Syringe
Strength	5 mg	25 mg	0 mg (for 5 mg)	0 mg (for 25 mg)	200 mg	180 $\mu$ g/ 0.5 mL
Bulk lot number	10-004948	10-004949	10-004734	10-004735	09-026055	10-005665

<p><b>Duration of Treatment:</b> Study drug (ABT-267 or placebo + pegIFN/RBV) was administered for up to 12 weeks followed by 36 weeks of pegIFN/RBV alone.</p>
<p><b>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</b> Not applicable.</p>
<p><b>Criteria for Evaluation</b></p> <p><b>Efficacy:</b> The primary efficacy endpoint was the percentage of all dosed subjects with RVR (HCV RNA suppressed below the LLOD at Week 4). The secondary efficacy endpoints were: 1) the percentage of subjects with pEVR (HCV RNA decrease &gt; 2 log<sub>10</sub> IU/mL at Week 12) and the percentage of subjects with cEVR (HCV RNA &lt; LLOQ at Week 12), 2) the percentage of subjects with SVR 12 weeks after the last dose of pegIFN/RBV (SVR<sub>12</sub>) and the percentage of subjects with SVR 24 weeks after the last dose of pegIFN/RBV (SVR<sub>24</sub>), 3) the time to suppression of HCV RNA (HCV RNA &lt; LLOQ), 4) the percentage of subjects with eRVR (HCV RNA &lt; LLOQ at Week 4 and Week 12, with no confirmed detectable HCV RNA in between), 5) the exposure-response relationship between ABT-267 concentrations and antiviral efficacy could have been explored by combining data from this study with other Phase 2 and/or Phase 3 studies and provided in a separate report.</p> <p>The presence of resistance-associated variants in NS5A prior to treatment and the emergence of resistance-associated variants in NS5A over time were assessed. The degree of phenotypic resistance (fold change in susceptibility compared to wild-type virus) to ABT-267 was also assessed.</p> <p>The change from baseline in nondisease-specific health-related quality of life (HRQoL), disease-specific HRQoL, and Health State Utility were measured using the generic short form 36 question health survey (SF-36) instrument, disease-specific HCV patient-reported outcome (HCVPRO) instrument, and the European Quality of Life-5D 3 Level Health (EQ-5D) Survey, respectively. The HRQoL score and health state utility were measured and analyzed for change with respect to time, treatment, and response.</p> <p><b>Pharmacokinetic:</b> Plasma concentrations of ABT-267, possible ABT-267 metabolites, and RBV and serum concentrations of interferon were summarized.</p> <p><b>Safety:</b> Safety was evaluated based on adverse events, clinical laboratory determinations, vital signs, physical examination, and 12-lead electrocardiogram.</p>
<p><b>Statistical Methods</b></p> <p><b>Efficacy:</b> For the primary endpoint, the percentage of subjects with RVR was compared between each ABT-267 group and the placebo group using logistic regression with treatment group, baseline HCV RNA level, HCV subgenotype (1a or 1b), and interleukin 28B (IL28B) genotype (CC, non CC) as predictors.</p>

### **Statistical Methods (Continued)**

#### **Efficacy (Continued):**

Mean changes in HCV RNA from baseline to all visits (HCV RNA assessed in each subject through 24 weeks post-pegIFN/RBV treatment) were summarized with the baseline mean, visit mean, change from baseline mean, standard deviation, median, and range. The imputation of missing values between flanking undetectable was not performed in the change from baseline analyses. The percentage of subjects with undetectable HCV RNA at each visit during ABT-267/placebo treatment was summarized both in an ITT analysis where subjects missing data at the visit counted as failures and an on-treatment analysis where subjects missing data at the visit were excluded from the analysis. Similar analyses of the percentage of subjects with undetectable HCV RNA at each post-ABT-267/placebo treatment visit were calculated.

The development of resistance during treatment was assessed by calculating the fold change in EC<sub>50</sub> levels at each postbaseline time point compared both to baseline and prototypic standards. The fold changes at each time point were summarized for each treatment group, and were compared between each ABT-267 group and the combined placebo group using Wilcoxon rank sum tests.

The amino acid changes in mixed population sequencing for each treatment group 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 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, and amino acid changes for population and clonal sequencing were summarized for these signature mutations within each treatment group and within each subject, respectively.

The frequency of subjects in each treatment group with an emerged or enriched mutation from baseline was summarized by amino acid position; a subject was considered to have emerged/enriched mutation if at any time point with clonal sequencing performed after baseline the increase from baseline in percentage of clones of any variant was greater than or equal to 20% and was detected in at least 2 subjects of the same subgenotype.

#### **Pharmacokinetic:**

Individual plasma concentrations of ABT-267, possible ABT-267 metabolites, and ribavirin and serum concentrations of IFN at scheduled collection times and study visits were tabulated and summarized using appropriate statistical methods.

For ABT-267, the area under the concentration-time curve (AUC) until 8 hours after study drug administration (AUC<sub>8</sub>) on Day 1 was determined across all subjects, and AUC until 24 hours after study drug administration (AUC<sub>24</sub>) on Day 1 was determined only for those subjects who returned to the study sites on Day 2 for pharmacokinetic sample collection prior to study drug administration on Day 2.

**Statistical Methods (Continued)**

**Pharmacokinetic (Continued):**

The plasma concentrations of ABT-267 and ribavirin were also summarized based on the time after the last dose for the pharmacokinetic samples collected at study visit from Weeks 2 through 12, as both ABT-267 and ribavirin were expected to achieve steady-state 2 weeks after dosing. For this analysis, plasma concentrations were binned based on the following time after dose intervals for ABT-267: 0–3, > 3–6, > 6–9, > 9–12, > 12–15, > 15–18, > 18–22, > 22–26, and > 26 hours and ribavirin: 0–2, > 2–4, > 4–6, > 6–10, > 10–14, and > 14 hours. If there were multiple observations from a subject in a particular bin, an average was computed. A summary of ABT-267 and ribavirin concentrations across subjects in each bin was computed.

The exposure-response relationship between ABT-267 concentrations and antiviral efficacy could be explored by combining data from this study with other Phase 2 and/or 3 studies and provided in a separate report.

**Safety:**

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 15.1). The number and percentage of subjects in each treatment group having treatment-emergent adverse events were tabulated by primary MedDRA System Organ Class and preferred term and compared between each ABT-267 group and the placebo group using Fisher's exact tests. The tabulation of the number of subjects with treatment-emergent adverse events was also provided with further breakdown by severity rating and relationship to ABT-267, RBV, and pegIFN.

Clinical laboratory tests were summarized by treatment group at each visit during Substudy 1. 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 differences between each ABT-267 group and the placebo group were analyzed using contrasts within an analysis of variance (ANOVA) model with treatment group as the factor. 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 treatment group. In addition, the number and percentage of subjects with postbaseline values meeting prespecified criteria for Potentially Clinically Significant (PCS) laboratory values were summarized by treatment group. Comparisons were performed between each ABT-267 group and the placebo group for 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 during Substudy 1 were summarized descriptively for each treatment group and were compared between each ABT-267 group and the placebo group using contrasts within an ANOVA model with treatment group as a factor. Frequencies and percentages of subjects with postbaseline values meeting predefined criteria for PCS vital sign values were summarized. Comparisons of the percentage of subjects with PCS vital sign criteria between each ABT-267 group and the placebo group were performed using Fisher's exact tests.

## Summary/Conclusions

### Efficacy Results:

Subjects were administered placebo or ABT-267 at 5 mg, 50 mg, or 200 mg QD for 12 weeks with pegIFN/RBV. Treatment with pegIFN/RBV continued for an additional 36 weeks after the last dose of ABT-267 or placebo. HCV RNA levels were monitored for 48 weeks after the last dose of ABT-267 or placebo and through 24 weeks post-pegIFN/RBV treatment. Results for the primary efficacy endpoint showed that HCV RNA levels were < LLOD at Week 4 for 2/9 (22.2%) subjects in the placebo group, 3/9 (33.3%) subjects in the 5 mg group, 5/9 (55.6%) subjects in the 50 mg group, 7/10 (70.0%) subjects in the 200 mg group, and 15/28 (53.6%) subjects in the combined ABT-267 group. The percentage of subjects achieving the primary endpoint in the 200 mg group was statistically significantly greater than in the placebo group ( $P = 0.030$ ). The primary efficacy endpoint was also analyzed by baseline HCV RNA level, gender, race, age, ethnicity, HCV genotype, IL28B genotype, baseline homeostasis model of assessment – insulin resistance, weight, and baseline IP-10. Subgroup sample sizes were too small for meaningful statistical analysis. However, results for the combined ABT-267 group showed that the majority of subjects achieved HCV RNA < LLOD at Week 4 for most subgroups.

The percentage of subjects achieving each secondary endpoint was greater in each ABT-267 group compared with placebo. Results for the placebo and combined ABT-267 group, as well as any statistically significant difference versus placebo, are as follows:

1. At Week 12, pEVR (a decrease in HCV RNA from baseline of  $> 2 \log_{10}$  IU/mL) was achieved by 7/9 (77.8%) subjects in the placebo group and 26/28 (92.9%) subjects in the combined ABT-267 group. The difference was statistically significant ( $P = 0.037$ ).
2. At Week 12, cEVR (HCV RNA < LLOQ) was achieved by 6/9 (66.7%) subjects in the placebo group and 25/28 (89.3%) subjects in the combined ABT-267 group.
3. SVR<sub>12</sub> (HCV RNA < LLOQ 12 weeks after the last dose of pegIFN/RBV) was achieved by 3/9 (33.3%) subjects in the placebo group and 18/28 (64.3%) subjects in the combined ABT-267 group.
4. SVR<sub>24</sub> (HCV RNA < LLOQ 24 weeks after the last dose of pegIFN/RBV) was achieved by 2/9 (22.2%) subjects in the placebo group and 14/28 (50.0%) subjects in the combined ABT-267 group.
5. Median time to virologic suppression (HCV RNA < LLOQ) was statistically significantly ( $P \leq 0.05$ ) shorter for the 5 mg group (27.0 days), 50 mg group (16.0 days), and combined ABT-267 group (21.5 days) compared with the placebo group (84.0 days).
6. eRVR (HCV RNA < LLOQ at Weeks 4 through 12) was achieved by 2/9 (22.2%) subjects in the placebo group and 22/28 (78.6%) subjects in the combined ABT-267 group. The percentage of subjects achieving eRVR was statistically significantly greater for the 5 mg group ( $P = 0.028$ ), 200 mg group ( $P = 0.021$ ), and combined ABT-267 group ( $P = 0.020$ ) compared with the placebo group.

Patient-reported outcomes were also assessed in this study by a self-administered generic SF-36 instrument, disease-specific HCVPRO instrument, and the EQ-5D health state utility instrument. No statistically significant differences were observed between the placebo group and any ABT-267 treatment group.

### **Summary/Conclusions (Continued)**

#### **Efficacy Results (Continued):**

Baseline samples from 28 subjects in the ABT-267 treatment groups and 8 subjects in the placebo group were analyzed for the presence of resistance-associated variants. Three genotype 1a subjects had baseline variants at resistance-associated amino acid positions 28, 31, and/or 58, while 3 genotype 1b subjects had baseline variants at resistance-associated amino acid positions 30, 31, and/or 93. However, the presence of baseline variants did not impact the treatment outcome in any of these subjects, as none of them experienced virologic failure.

On Day 3, Day 7, or Week 2 of ABT-267 + pegIFN/RBV treatment, 5 of 9 subjects in the 5 mg group, 4 of 9 subjects in the 50 mg group, and 4 of 10 subjects in the 200 mg group had at least 1 sample with HCV RNA  $\geq$  1,000 IU/mL, allowing for resistance analyses to be conducted. In genotype 1a, the predominant resistance-associated variants that were observed in subjects at time points during the first 2 weeks of treatment with ABT-267 were M28T, M28V, Q30R, H58D, Y93C, and Y93H in genotype 1a. The M28V variant, which confers 58-fold resistance to ABT-267, did not appear in the genotype 1a subjects dosed with 50 or 200 mg of ABT-267. All other genotype 1a resistance-associated variants conferred more than 800-fold resistance to ABT-267. In genotype 1b, the predominant resistance associated variant that was observed at time points during the first 2 weeks of treatment with ABT-267 in 2 of the 5 subjects was Y93H, either alone or in combination with R30Q or L31M; resistance-associated variants were not detected in 3 of the genotype 1b-infected subjects. The Y93H variant in genotype 1b conferred 77-fold resistance to ABT-267, and when variant R30Q or L31M was added, an additional 2- to 4- fold resistance was observed relative to that conferred by Y93H alone.

Resistance analyses were conducted on 6 subjects in the ABT-267 treatment groups that experienced virologic failure. Two of the subjects (4034 and 4008) experienced breakthrough while on ABT-267 + pegIFN/RBV treatment. Subjects 4016, 4059, and 4069 experienced virologic failure subsequent to treatment with ABT-267; HCV RNA was not suppressed in Subject 4025 during treatment with ABT-267. In the genotype 1a-infected subjects (4016, 4034, 4059, and 4025) experiencing virologic failure, the predominant variants were M28T, M28V (5 mg dose group only), Q30R, and H58D, with M28T and H58D persisting up to 48 weeks post-ABT-267 treatment. The in vitro replication fitness of the Y93C/H variants was less than 20% while all other resistance-associated variants had greater than 60% replication efficiency, which could explain the persistence of variants at amino acid positions 28, 30, and 58 in genotype 1a. In the genotype 1b-infected subjects (4069 and 4008) experiencing virologic failure, the predominant resistance-associated variants were P29 deletion, Y93H, and double variants at positions 58 and 93. The predominant variants that persisted out to Post-ABT-267 Week 48 in the single available sample from a genotype 1b-infected subject were P58S and Y93H. The in vitro replication fitness of the P29deletion and the double variants was less than 35%, whereas the P58S and Y93H variants had greater than 70% replication efficiency, which could explain the persistence of single variants at amino acid positions 58 and 93 in genotype 1b.

#### **Pharmacokinetic Results:**

ABT-267 plasma concentrations reached steady state after about 1 to 2 weeks of dosing, which is consistent with the half-life of 28 to 34 hours following multiple dosing that was observed in a previous Phase 1 study (M12-116). Consistent with their long half-lives, plasma concentrations of RBV and pegIFN reached steady state after about 2 to 4 weeks of dosing. Both RBV and pegIFN concentrations were comparable among the 5 mg, 50 mg, and 200 mg doses of ABT-267, suggesting a lack of effect of ABT-267 on RBV and pegIFN pharmacokinetics.

**Summary/Conclusions (Continued)**

**Safety Results:**

The majority of subjects were compliant with ABT-267/placebo, RBV, and pegIFN. Mean duration of treatment with placebo and ABT-267 were 84.7 days and 80.1 days, respectively. No deaths, serious adverse events, or adverse events leading to discontinuation of study drug were reported during the study. At least 1 treatment-emergent adverse event was experienced by 9 (100%) subjects who received placebo and 26 (92.9%) subjects who received ABT-267. The most frequently reported ( $\geq 20.0\%$  of subjects) treatment-emergent adverse events were fatigue, nausea, vomiting, influenza like illness, headache, anxiety, insomnia, and rash among subjects who received placebo and fatigue, nausea, headache, vomiting, pain, anemia, chills, and rash among subjects who received ABT-267. The percentage of subjects with adverse events reported in the combined ABT-267 group was not statistically significantly greater than the placebo group for any event ( $P \geq 0.05$ ). Many of the most frequent adverse events seen in the ABT-267 treatment groups are consistent with the known safety profile of pegIFN and/or 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 standard MedDRA query were observed. Approximately half of subjects in each treatment group experienced an adverse event identified by the drug induced rash company MedDRA query. The majority of these events were mild in severity. Since RBV is associated with rash and pruritus, it is difficult to attribute these events with certainty to ABT-267.

Mean decreases were observed for hemoglobin and red blood cells in each treatment group at the end of treatment, which is consistent with the known effect of RBV. However, no subject had a hemoglobin value that met a PCS criterion during the study.

Mean decreases were observed for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) in each treatment group, which is indicative of viral clearance from the liver. No subject had an ALT or AST value that met a PCS criterion. Few subjects had transient elevations in total bilirubin (2 of 9 subjects in the placebo group and 3 of 28 in the combined ABT-267 group). PCS elevations in total bilirubin were experienced by 2 subjects who received ABT-267. No subject experienced a postbaseline ALT, AST, alkaline phosphatase, or total bilirubin value of grade  $\geq 3$ .

**Conclusions:**

A 12-week regimen of ABT-267 coadministered with pegIFN and RBV was well tolerated in HCV genotype 1-infected, treatment-naïve subjects. The primary endpoint (HCV RNA  $<$  LLOD at Week 4) was achieved by 2/9 (22.2%) subjects in the placebo group, 3/9 (33.3%) subjects in the 5 mg group, 5/9 (55.6%) subjects in the 50 mg group, and 7/10 (70.0%) subjects in the 200 mg group. These results justify continued evaluation of ABT-267 in patients with HCV genotype 1 infection.

**Date of Report:** 19Aug2013