Synopsis

<table>
<tr><td>Abbott Laboratories</td><td>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, ABT-333, ABT-072</td><td rowspan="2"></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
ABT-072: potassium 3-{3-tert-butyl-4-methoxy-5-[(E)-2-{4-[(methylsulfonyl)amino]phenyl}ethenyl] phenyl}-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide trihydrate
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: A Blinded, Randomized, Placebo-controlled, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of Multiple Doses of ABT-450 with Ritonavir (ABT-450/r), ABT-333 or ABT-072 Each Administered Alone and in Combination with Peginterferon α-2a and Ribavirin (PegIFN/RBV) in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection</td></tr>
<tr><td colspan="3">Coordinating Investigator: Dr. Fred Poordad, MD</td></tr>
<tr><td colspan="3">Study Site(s): 25 sites in the US and Puerto Rico</td></tr>
<tr><td colspan="3">Publications: 3 abstracts</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 02 March 2010
Last Subject Last Visit: 27 January 2012</td><td>Phase of Development: 2a</td></tr>
</table>

Objectives:

The primary objective of this study was to assess the safety, tolerability, pharmacokinetics, and antiviral activity of multiple oral doses of ABT-450/r, ABT-333, or ABT-072 each administered alone under nonfasting conditions for 3 days in HCV genotype 1-infected treatment-naïve adults.

The secondary objectives of this study were: to assess the safety, tolerability, pharmacokinetics, and antiviral activity of ABT-450/r, ABT-333, and ABT-072, each administered with pegIFN/RBV for 12 weeks, to assess the development and persistence of viral resistance to ABT-450, ABT-333, and ABT-072 and determine the impact of resistance on the kinetics of viral load decay and rebound in treatment-naïve HCV-infected subjects, to evaluate phenotypic resistance to the study drug in the in vitro subgenomic replicon system at serial time points and to correlate phenotypic resistance with specific patterns of mutations over time, and to assess HCV-specific health related quality of life (HCVQoL, now referred to as HCV patient-reported outcomes [PRO]) parameters, general HRQoL parameters, and health state utility (preference).

Methodology:

This was a Phase 2a, randomized, blinded, placebo-controlled, dose-ranging study enrolling up to 75 chronically HCV genotype 1-infected subjects at approximately 30 sites in the United States and Puerto Rico. The study was designed to explore the safety, tolerability, pharmacokinetics, and antiviral activity of ABT-450/r, ABT-333, or ABT-072 monotherapy for 3 days in HCV genotype 1-infected, treatment-naïve adult subjects followed by 81 days (12 weeks minus 3 days of monotherapy) of pegIFN/RBV added to ABT-450/r, ABT-333, or ABT-072, followed by 36 weeks of pegIFN/RBV therapy alone. With the second protocol amendment, subjects randomized to an ABT-450/r treatment group who achieved RVR and had HCV RNA < 25 IU/mL at all subsequent visits were eligible to stop pegIFN/RBV therapy on or after Study Week 24. The study was also designed to monitor and evaluate the evolution and persistence of resistance to ABT-450/r, ABT-333, and ABT-072 in HCV genotype 1-infected subjects.

Number of Subjects (Planned and Analyzed): 75 planned/74 analyzed

Diagnosis and Main Criteria for Inclusion:

The selection of subjects infected with HCV genotype 1 virus allowed for the assessment of safety and pharmacokinetics of daily dosing of ABT-450/r, ABT-333, or ABT-072 in HCV-infected treatment-naïve subjects, as well as an assessment of the antiviral activity of ABT-450/r, ABT-333, or ABT-072 alone and in combination with pegIFN/RBV. Subjects who had received prior treatment for their HCV infection, including experimental HCV therapy, were excluded from participation as the effect on ABT-450/r, ABT-333, or ABT-072 antiviral activity when administered as monotherapy or when coadministered with pegIFN/RBV may be impacted. This study restricted enrollment to HCV genotype 1-infected subjects who had no evidence of advanced liver disease, thereby limiting risk of unanticipated pharmacokinetics or other adverse effects not observed in prior dosing in healthy volunteers.

Diagnosis and Main Criteria for Inclusion (Continued):

HCV-infected subjects with transaminase levels up to 5 times the upper limit of normal (ULN) were allowed to enroll, as many otherwise healthy patients with chronic HCV infection have stable elevations levels of AST and ALT levels and were considered representative of the population who would receive ABT-450/r, ABT-333, or ABT-072. The age range selected for this study, 18 through 65 years, was also intended to be representative of the target population. Similarly, a substantial portion of the HCV-infected population has a relatively high BMI. Because of the acceptable safety and pharmacokinetic profiles of ABT-450/r, ABT-333, and ABT-072 in Phase 1 studies, this protocol enrolled subjects with a BMI up to 35 kg/m^2.

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

The study drug regimens were ABT-450/r 50/100, 100/100, and 200/100 mg QD, ABT-072 100 and 300 mg QD, ABT-333 400 and 800 mg BID, pegIFN 180 µg SC once a week, and weight based RBV 1000 to 1200 mg PO divided twice daily.

DAA study drugs were provided for oral administration as follows: ABT-450 50 mg hard gelatin capsule (bulk lot number 09-026133 and matching placebo bulk lot 09-026231); coadminstered ritonavir 100 mg soft gelatin capsules (bulk lot number 09-021003 and matching placebo bulk lot 09-021002); ABT-072 50 mg tablet (bulk lot number 09-025077 and matching placebo bulk lot 09-025078); and ABT-333 400 mg tablet (bulk lot number 10-000479 and matching placebo 09-021448).

RBV was provided as a 200 mg tablet (bulk lot number 09-026055) for oral administration.

pegIFN was provided as a 180 µg/0.5 mL subcutaneous injection (bulk lot number 09-022735 and 09-025410).

Duration of Treatment: 3 days of DAA monotherapy, 81 days of combination DAA and pegIFN/RBV therapy, followed by up to an addition 36 weeks of pegIFN/RBV therapy.

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

Not applicable.

Criteria for Evaluation

Efficacy:

The primary efficacy endpoint was the maximal decrease from baseline in $\log_{10}$ HCV RNA levels during ABT-450/r or ABT-333 or ABT-072 monotherapy treatment (through prior to Study Day 4 morning dose). The secondary efficacy endpoints were the percentage of subjects with RVR (HCV RNA level < 25 IU/mL at Study Week 4) and the percentage of subjects with partial EVR (HCV RNA decrease of > 2 $\log_{10}$ IU/mL at Study Week 12) or complete EVR (HCV RNA < 25 IU/mL at Study Week 12 with ABT-450/r or ABT-333 or ABT-072 or placebo).

Resistance:

The presence of resistance-associated variants in the relevant target gene prior to treatment and the emergence of resistance-associated variants in the relevant target gene over time were assessed. The degree of phenotypic resistance (fold change in susceptibility compared to wild-type virus) to the study drug was also assessed.

Criteria for Evaluation (Continued)

Health-Related Quality of Life Measures:

The change in disease-specific HRQoL, generic HRQoL, and Health State Utility was measured using the HCVQoL, SF-36, and EQ-5D, respectively. Each instrument had been validated for this use. HRQoL score and health state utility were measured and analyzed for change with respect to time, treatment, and response.

Pharmacokinetic:

Values for the pharmacokinetic parameters of ABT-450, ritonavir, ABT-072, ABT-333, and ABT-333 M1 metabolite including the C_{max}, T_{max} and AUC were determined for the dosing intervals on Study Days 1 and 3 by noncompartmental methods using Phoenix™ WinNonlin®, Version 6.1 (Pharsight Corporation, Mountain View, CA). For ABT-450, ritonavir and ABT-072 the concentration at 24 hours (C_{24}) was taken directly from the concentration time data. For ABT-333 and metabolite M1 the concentration at 12 hours (C_{12}) was the concentration following the morning dose. Dose-normalized C_{max}, C_{24}, and AUC values were also calculated by dividing each of the pharmacokinetic parameters by the administered dose.

Safety:

The following safety evaluations were performed during the study: adverse event monitoring, vital signs, physical examination, ECG, and laboratory tests assessments.

Statistical Methods

Efficacy:

For the efficacy endpoints specified below, pairwise comparisons among the ABT-450/r dose groups (i.e., Groups A, C, and E) and the placebo group, between the ABT-072 dose groups (i.e., Groups G, I and K) and the placebo group, and between the ABT-333 dose groups (i.e., Groups M and O) and the placebo group were made. No adjustment for multiple endpoints, timepoints, or comparisons was made in this pilot study. Additional comparisons may have been included in post-pegIFN/RBV analyses for the subjects treated with ABT-450/r who were eligible and opted to stop treatment with pegIFN/RBV prior to Study Week 48.

The primary efficacy endpoint was the maximum decrease from baseline in $\log_{10}$ HCV RNA levels during ABT-450/r, ABT-333, or ABT-072 monotherapy treatment (through prior to Study Day 4 morning dose).

The baseline value was the last measurement before the first dose on Study Day 1. The maximal decrease during monotherapy was the change from baseline to the lowest $\log_{10}$ HCV RNA level anytime after the first dose of study drug on Study Day 1 through the last $\log_{10}$ HCV RNA level before the first dose of study drug on Study Day 4. For each treatment group, the endpoint was summarized descriptively using N, mean, median, standard deviation, and range. The maximum decrease was summarized and compared among appropriate treatment groups using contrasts within a 1-way analysis of covariance (ANCOVA), with treatment group as the factor and including $\log_{10}$ baseline HCV RNA level as a covariate.

Statistical Methods (Continued)

Efficacy (Continued):

The percentage of subjects with RVR in viral load at Study Week 4 and complete or partial EVR in viral load at Study Week 12 or at the Final Treatment (DAA study drug) Visit was compared among treatment groups using Fisher's exact tests.

An additional efficacy endpoint was the percentage of subjects with SVR (HCV RNA level < lower limit of detection at Study Week 72). The percentage of subjects with SVR was compared among treatment groups using Fisher's exact tests.

The exposure-response relationships between ABT-450/r, ABT-072, or ABT-333 concentrations and pharmacodynamics (antiviral efficacy) were explored.

Subgroup analyses of the primary and secondary efficacy endpoints were performed by HCV subtype (1a or 1b) and by IL28B genotype (CC, TC or TT).

Resistance:

The presence of resistance-associated variants in the relevant target gene prior to treatment and the emergence of resistance-associated variants in the relevant target gene over time were summarized. If appropriate, the variants may have been summarized within subgroups of study drug-treated subjects defined by dose, duration of dosing, and/or concomitant therapy. The degree of phenotypic resistance was assessed by calculating the fold change in EC50 levels for ABT-450, ABT-333, and ABT-072 at each postbaseline timepoint tested compared to both baseline and the appropriate prototypic reference standard. For each compound, the fold changes at each timepoint were summarized descriptively by treatment group and tests of differences between appropriate groups were performed using Kruskal-Wallis tests.

If sufficient data were available, the relationship between specific target gene resistance mutations and the degree of phenotypic resistance to study drug may have been analyzed using logistic regression or other appropriate methods.

Health-Related Quality of Life Measures:

The impact of drug administration on subjects' health related quality of life PROs was assessed by a self-administered generic SF-36 instrument (36 items), disease specific HCVQoL instrument (16 questions), and the EQ-5D health state utility instrument (5 items plus 1 VAS) at Study Days –1 (baseline) and 18, and Study Weeks 4, 8, 12, 24, 36, 48/EOT and PTW 24. On Study Day 4, only the EQ-5D VAS was administered.

Statistical Methods (Continued)

Patient-Reported Outcomes:

The mean change from baseline (Study Day –1) to Study Day 18 and Study Weeks 4, 8, 12, 24, 36, 48/EOT and PTW 24 in HCVQoL and SF-36 scores was calculated. Subject's responses to the self-administered HCVQoL instrument were assessed for each item individually and for the total score. Subject's responses to the SF-36 were summarized for the 8 domains and Physical Component Summary and Mental Component Summary measures. Summary statistics (N, mean, SD, median, minimum and maximum) by treatment group were provided for each item and for the total score for the HCVQoL and the 8 domains and the physical and mental health summary measures for the SF-36. Subject's responses to the EQ-5D 5 dimensions were combined into a unique health state using a 5 digit code with 1 digit from each of the 5 dimensions. The EQ-5D states were converted into a single preference-weighted health index score by applying appropriate scoring algorithm for different populations. The mean change from baseline (Study Day –1) to Study Day 18 and Study Weeks 4, 8, 12, 24, 36, 48/EOT and PTW 24 in EQ-5D health index score and VAS score was calculated. Summary statistics (N, mean, SD, median, minimum and maximum) by treatment group were provided for the health index score and VAS score.

A repeated-measures ANCOVA analysis was performed on the change from baseline in HCVQoL total score and EQ-5D health index score with fixed effects for treatment group, the day of measurement, and possibly the 2-way interaction between treatment group and day, subject as a random effect, and baseline score as a covariate (other covariates including baseline $\log_{10}$ HCV RNA levels may have been included). Regression analysis with the appropriate QoL summary measure as dependent variable and HCV viral load as independent variable (other factors may be included) was be performed to examine the relationship between those 2 measurements.

Pharmacokinetics:

Plasma concentrations of ABT-450, ritonavir, ABT-333, ABT-072, and possible metabolites and pharmacokinetic parameters were tabulated for each subject and dose group. Summary statistics were computed for each sampling time and each parameter.

A repeated measure analysis was performed for the natural logarithms of dose normalized C_{max} and AUC on Study Days 1 and 3 for ABT-450, ritonavir, ABT-072, ABT-333 and ABT-333 metabolite. The model had subject as a random effect. The model also included effects for regimen, study day, and the interaction between regimen and study day. Body weight, sex, age, and smoking status were considered as possible covariates. A necessary condition for such covariate variables to be included in the final model was that the regression coefficient was significant at level 0.10. For analyses on ABT-450, body weight and sex were included in the final model. For analyses on ritonavir, sex and smoking status were included as covariates. For analyses on ABT-072 and ABT-333 metabolite, body weight was included as covariate. For analyses on ABT-333 age and body weight were included in the final model. For ABT-450, the primary test of the hypothesis in invariance with dose (i.e., the hypothesis of dose proportionality or linear kinetics) was performed on an appropriate contrast in the dose level effects and tests were performed for each study day. The pairwise comparisons between regimens on each study day were also performed to provide additional information. The primary test for ritonavir was performed on the comparison of different regimens within the framework of mixed model.

Statistical Methods (Continued)

Safety:

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

Adverse events were coded using MedDRA. The number and percentage of subjects in each treatment group having treatment-emergent adverse events (i.e., any event that began or worsened in severity after initiation of randomized study drug through 30 days postdosing) with ABT-450, ABT-333, ABT-072 or matching placebo (for any) was tabulated by primary MedDRA System Organ Class and preferred term and compared among appropriate treatment groups using Fisher's exact tests. The tabulation of the number of subjects with treatment-emergent adverse events also was provided with further breakdown by severity rating and relationship to DAA study drug, pegIFN, or RBV. Subjects reporting more than 1 adverse event for a given MedDRA preferred term were counted only once for that term using the most severe incident for the severity rating table and the most related for the relationship to study drug table. Subjects reporting more than 1 type of event within a System Organ Class were counted only once for that System Organ Class.

Mean changes from baseline in clinical laboratory tests were summarized by treatment group 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 and treatment group differences between appropriate groups were analyzed using contrasts within an 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 percent of subjects 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 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 and all groups. Comparisons were performed among the appropriate treatment groups of 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 descriptively and appropriate treatment group differences were analyzed using contrasts within an ANOVA model with treatment group as factor. Frequencies and percentages of subjects 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 between treatment groups were performed using Fisher's exact tests.

Summary/Conclusions

Efficacy Results:

ABT-450/r, ABT-072, and ABT-333 were administered alone for 3 days and with pegIFN and RBV for 81 days (for a total of 12 weeks) and HCV RNA levels were monitored through 48 weeks post-DAA treatment. For the primary efficacy endpoint of maximum decrease from baseline in $\log_{10}$ HCV RNA levels during ABT-450/r or ABT-333 or ABT-072 monotherapy treatment, subjects who received ABT-450/r monotherapy (N = 24) had a mean maximum 4.03 $\log_{10}$ IU/mL HCV RNA decline, subjects who received ABT-072 monotherapy (N = 23) had a mean maximum 1.25 $\log_{10}$ IU/mL HCV RNA decline, and subjects who received ABT-333 monotherapy (N = 16) had a mean maximum 1.02 $\log_{10}$ IU/mL HCV RNA decline compared to a 0.36 $\log_{10}$ IU/mL HCV RNA decline with placebo (N = 11), $P < 0.016$ for each pair wise comparison to placebo.

The primary efficacy endpoint was also analyzed by HCV subtype and IL28B genotype as specified in the protocol. Among all 3 ABT-450/r dose groups, the mean maximum HCV RNA decreases were both statistically significantly different from the placebo group in HCV subtype 1a and 1b subjects. Due to the small number of subjects enrolled with HCV genotype 1b, it is difficult to make a meaningful comparison of treatment response by HCV subgenotype. However, it generally appears that ABT-450/r has similar potency on subjects with HCV genotype 1a and 1b infection, while ABT-072 and ABT-333 are less potent in subjects with HCV genotype 1a infection. With regard to IL28B genotype, no differences were seen in treatment response among subjects with C/C, C/T, or T/T genotype. Overall, ABT-450/r is shown to have similar potency in the more difficult to treat subjects with HCV subtype 1a and IL28B non-CC genotype.

For the secondary efficacy endpoints, 21 of 24 subjects (87.5%) who received ABT-450/r, 8/16 subjects (50.0%) who received ABT-333, 7/23 subjects (30.4%) who received ABT-072, and 1/11 (9.1%) of subjects who received placebo achieved RVR at Study Week 4. The RVR rates for all subjects who received ABT-450/r, all subjects who received ABT-333, and all subjects who received ABT-072 were each statistically significantly different from placebo ($P < 0.042$). Additionally, 23 of 24 subjects (95.8%) who received ABT-450/r, 16/16 subjects (100.0%) who received ABT-333, 20/23 subjects (87.0%) who received ABT-072, and 4/11 (36.4%) of subjects who received placebo achieved partial EVR at Study Week 12. The partial EVR rates for all subjects who received ABT-450/r, all subjects who received ABT-333, and all subjects who received ABT-072 were each statistically significantly different from placebo ($P < 0.005$). Finally, 22 of 24 subjects (91.7%) who received ABT-450/r, 12/16 subjects (75.0%) who received ABT-333, and 16/23 subjects (69.6%) who received ABT-072, and 2/11 (18.2%) of subjects who received placebo achieved complete EVR at Study Week 12. The complete EVR rates for all subjects who received ABT-450/r, all subjects who received ABT-333, and all subjects who received ABT-072 were each statistically significantly different from placebo ($P < 0.009$).

In addition to the primary and secondary efficacy variables, values for SVR_{12} and SVR_{24} were determined. Twenty of 24 subjects (83.3%) who received ABT-450/r, 12/23 subjects (52.2%) who received ABT-072, 10/16 subjects (62.5%) who received ABT-333, and 1/11 (9.1%) of subjects who received placebo achieved SVR_{12} and SVR_{24}. The SVR_{12} and SVR_{24} rates for all subjects who received ABT-450/r, all subjects who received ABT-333, and all subjects who received ABT-072 were each statistically significantly different from placebo ($P \leq 0.024$). While sample size limits interpretation, a trend was noted suggesting higher ABT-450 doses were associated with higher SVR rates. Overall, 1 subject who received placebo, 3 subjects who received ABT-450/r, 3 subjects who received ABT-072, and 3 subjects who received ABT-333 relapsed after completion of DAA or placebo treatment.

Summary/Conclusions (Continued)

Resistance Results:

ABT-450

No subjects in the ABT-450-treated groups had resistance-associated variants in HCV N3 protease prior to treatment. Three of the 4 subjects who did not achieve SVR_{24} had resistance-associated variants detected by clonal sequencing in NS3 at the time of virologic failure. One subject had the NS3 D168V amino acid variant present in the first postfailure sample available for resistance analysis but no resistance-associated variants were present in subsequent samples analyzed by clonal sequencing. In a second subject, resistance-associated amino acid variant R155K was detected in NS3 after virologic relapse, and this variant persisted to Post-Treatment Week 24. The third subject achieved a ~4.0 log_{10} HCV RNA decline at the end of the 3-day monotherapy but there was a plateau in viral load during continued dosing with ABT-450 + pegIFN/RBV. The resistance-associated variant R155K was detected in NS3 protease, accompanied by variants at amino acid positions 36 and 132 while the subject was on active treatment with ABT-450 + pegIFN/RBV. A subject who experienced virologic relapse 24 weeks post-treatment had no NS3 resistance-associated amino acid variants present. Phenotypic analysis demonstrated that the presence of the D168V variant in failure samples led to > 100-fold increase in resistance to ABT-450, whereas the R155K variant conferred lower level resistance.

ABT-072

One of 23 subjects in the ABT-072-treated groups had a resistance-associated amino acid variant prior to treatment. This subject had an S556G amino acid variant in NS5B, associated with a phenotypic resistance of 13.4-fold relative to prototypic reference. Eleven of the 23 subjects in the ABT-072 treatment groups did not achieve SVR_{24}. Amino acid variants at signature resistance-associated positions emerged in 8 of the 9 subjects who experienced virologic failure for whom samples were available. The most common variants were: M414T or M414I in 5 subjects; and S556G in 5 subjects. The amino acid variant C316Y was observed in 3 subjects, and was associated with a high degree of phenotypic resistance.

Upon completion of the DAA therapy, the prevalence, determined by clonal sequencing, of the C316Y variant decreased, associated with decreasing phenotypic resistance. In 3 subjects, variants at high prevalence persisted post-DAA therapy. These variants (Y448H, G554S, and S556R) were associated with phenotypic resistance in these subjects. M414 and S556 variants were also found to persist, but were associated with low level resistance in subjects treated with ABT-072.

ABT-333

Three of 16 subjects in the ABT-333-treated groups had a resistance-associated amino acid variant in NS5B prior to treatment. Two subjects had an S556G amino acid variant in NS5B, and one subject had an M414I variant. These variants confer low level resistance to ABT-333 as determined by phenotype analysis of these subjects' HCV samples. All 3 of these subjects achieved SVR_{24}. After 3 days of monotherapy with ABT-333, phenotypic resistance in all subjects was unchanged from that of the baseline samples. Resistance-associated variants at amino acid 556 were most common among subjects at the end of monotherapy.

Six subjects, 3 from each of the ABT-333 dose groups, did not achieve SVR_{24}. Upon relapse, or with plateau of viral load during continued dosing with ABT-333 and pegIFN/RBV, increased phenotypic resistance was measured, along with an increase in the prevalence of resistance-associated amino acid variants. S556G was the dominant resistance-associated variant in samples from subjects who experienced virologic failure, and the prevalence of this variant was maintained after the end of ABT-333 treatment.

Summary/Conclusions (Continued)

Patient-Reported Outcomes Results:

HCV-PRO mean total score was greater than 70 points (range: 72 to 86) at baseline in each of the treatment groups, indicating relatively good function and wellbeing of treated subjects at study entry. The HCV-PRO total score declined progressively through treatment, with a -8 (placebo) to -16 (ABT-333) point decline at EODT and generally reaching a nadir at Post-DAA Week 24 (range: –11 to 26). The decline reached a plateau to EOT in DAA treatment groups. Decline at EOT was greatest in the ABT-450 group (–27.4). However, the placebo group exhibited only a –1.88 point decline at EOT, reflecting variability in the results. At Post-Treatment Week 24, the HCV-PRO total score in the placebo group was –9 points but had returned to approximately baseline values in all DAA treatment groups. Repeated measures ANCOVA showed statistical significance for HCV-PRO total score decline compared to placebo only in the ABT-450 group ($P = 0.024$).

EQ-5D VAS and EQ-5D Health Index scores showed response patterns generally similar to the HCV-PRO but with some variability over time. Baseline scores for the EQ-5D VAS were approximately 80 points in all treatment groups, indicating a healthy and functioning trial population. As with the HCV-PRO, the impact of therapy on EQ-5D VAS in each treatment group was a progressive decline in score through EODT (range: –1.9 to –10.1). Greatest impact on EQ-5D VAS was seen at EOT: ABT-450/r group exhibited the greatest decline from baseline (–14.1) while placebo and ABT-333 groups were declined minimally (–0.4 and –1.9, respectively). At Post-Treatment Week 24, scores on the EQ-5D VAS remained numerically declined compared to baseline levels in all DAA treatment groups (range: –9.0 to –2.4) except the ABT-333 group in which the score improved by 11.2 points, the only group showing this result. EQ-5D Health Index scores declined consistently to EODT (range: –0.05 to –0.14) and the decline was numerically maximum at EOT (range: –0.06 to –0.21). The ABT-450/r group showed the greatest decline at this time point, consistent with other measures. At Post-Treatment Week 24, EQ-5D Health Index scores remained mildly declined across treatment groups (range: –0.02 to –0.09). Repeated measures ANCOVA did not reveal statistical significance for any treatment group repeated-measures change score compared to placebo for either EQ-5D VAS or EQ-5D Health Index.

SF-36 PCS and MCS scores also showed response patterns similar to the HCV-PRO. The SF-36 PCS and MCS scores at baseline were close to population norms, for example, and the impairment in each SF-36 component score at baseline compared to population norms did not reach the threshold of minimally important difference (MID). As with the HCV-PRO, the impact of therapy in each treatment group was a progressive decline in instrument scores, reaching a nadir at EODT (PCS/MCS range: –4.8 to –7.6/–6.3 to –9.7, respectively) and remaining depressed at a plateau through to EOT (PCS/MCS range: –1.3 to –8.4/–6.3 to –16.5, respectively). Treatment group ABT-450/r exhibited the greatest decline, notably on the SF-36 MCS (–16.5), which is consistent with results from other instruments. Scores on the SF-36 PCS and MCS returned to near baseline levels or numerically better than baseline in all DAA treatment groups at Post-Treatment Week 24 except one; the MCS score was numerically reduced in the placebo group (–10.3) which may exceed the threshold of MID. Repeated measures ANCOVA did not reveal statistical significance for any treatment group change scores compared to placebo for SF-36 PCS/MCS.

These results of the health-related quality of life measures collectively indicate that the impact of interferon-based therapy predominates in the perception of patients under treatment. A signal can be associated with greater PRO score decline for the ABT-450/r + pegIFN/RBV group, although group size qualifies interpretation of these results. Patients returned to baseline levels of HRQoL function/wellbeing at 24 weeks post-treatment.

Pharmacokinetic Results:

ABT-450 at doses ranging from 50 to 200 mg given with 100 mg ritonavir showed greater than dose-proportional increases following monotherapy. Exposures for the 50 to 200 mg ABT-450 doses showed a supraproportional increase with dose. ABT-450 exposures were 80% to 310% higher on Day 3 compared to Day 1, consistent with the inhibitory effect of ritonavir seen in healthy subjects.

Ritonavir exposures were higher at the higher ABT-450 exposures on Day 1 similar to what has been observed in healthy subjects. However on Day 3 their was no clear trend as ritonavir exposure from the 200/100 mg dose group were comparable to the 100/100 mg dose group.

ABT-072 exposures on Day 1 and Day 3 were comparable indicating no accumulation at the 100 to 600 mg doses, consistent with the data in healthy subjects. Dose-normalized C_{max} and AUC_{24} values indicated that exposures increased in a slightly less than dose proportional manner with increasing ABT-072 doses.

ABT-333 exposures on Day 1 and Day 3 were comparable indicating no accumulation at the 400 and 800 mg BID doses, consistent with the data in healthy subjects. Dose-normalized C_{max} and AUC_{12} values indicated that exposures increased in a slightly less than dose proportional manner with increasing ABT-333 doses.

Safety Results:

A total of 74 subjects were exposed to study drug: 24 subjects received ABT-450/r, 23 subjects received ABT-072, 16 subjects received ABT-333, and 11 subjects received placebo. The full length of treatment was 84 days (3 days of DAA/placebo monotherapy followed by 81 days of DAA in combination with pegIFN/RBV). The median duration of treatment was 84 days for all DAA treatment groups (range: 5 to 94 days). All 74 subjects experienced at least 1 treatment-emergent adverse event during the study.

The most frequently reported (≥ 10% of subjects) DAA-related adverse events for subjects who received ABT-450/r were fatigue (25.0%), headache (25.0%), nausea (16.7%), rash (16.7%), depression (12.5%), dermatitis (12.5%), diarrhea (12.5%), and pruritus (12.5%). The frequency of subjects reporting DAA-related adverse events in the ABT-450/r group was not statistically significantly different from the placebo group for any event ($P \geq 0.05$).

The most frequently reported (≥ 10% of subjects) DAA-related adverse events for subjects who received ABT-072 were headache (47.8%), fatigue (21.7%), dizziness (17.4%), alopecia (13.0%), anemia (13.0%), cough (13.0%), and diarrhea (13.0%). The frequency of headache in the ABT-072 600 mg dose group was statistically significantly different as compared with the placebo group ($P = 0.047$).

The most frequently reported (≥ 10% of subjects) DAA-related adverse events for subjects who received ABT-333 were headache (31.3%), chills (18.8%), diarrhea (18.8%), fatigue (18.8%), dizziness (12.5%), nausea (12.5%), pyrexia (12.5%), and rash (12.5%). The frequency of subjects reporting DAA-related adverse events in the ABT-333 group was not statistically significantly different from the placebo group for any event ($P \geq 0.05$).

Many of the most frequent adverse events seen in all the DAA treatment groups are consistent with the known safety profile of pegIFN and/or RBV.

Safety Results (Continued):

The majority of adverse events reported for subjects who received DAA or placebo were mild or moderate in severity. There were no subjects who discontinued DAA during the study. One subject who received placebo discontinued the study due to adverse events (neck pain, back pain, and pain in extremity) and 2 subjects experienced non-DAA-related serious adverse events (hemorrhoids in a subject who received ABT-450/r and malignant melanoma in a subject who received ABT-072). No deaths were reported.

Statistically significant mean decreases from baseline to end of DAA treatment were observed for hemoglobin, hematocrit, red blood count, bands, and lymphocytes. A statistically significant difference in mean decrease from baseline to the end of DAA treatment for hemoglobin, hematocrit, and red blood count was noted for the ABT-333 800 mg BID group compared to placebo, but not for the ABT-333 400 mg BID group. Individual instances of hematologic laboratory abnormalities were either not considered clinically meaningful by the Sponsor medical monitor, or were managed with dose modification of pegIFN or RBV according to the protocol specifications for hematologic toxicity.

A statistically significant mean increase from baseline to end of DAA treatment was observed for ALP in the ABT-450/r 100/100 mg and 200/100 mg groups. This increase was small, typically in the Grade 1 range, not associated with adverse events or elevations of other liver enzymes, and resolved following DAA discontinuation. It was not considered clinically meaningful by the Sponsor medical monitor.

Mean changes from baseline for vital sign values were unremarkable and potentially clinically significant values were infrequent and generally considered not clinically meaningful by the Sponsor medical monitor.

Conclusions:

A 12-week regimen of ABT-450/r, ABT-072, or ABT-333 coadministered with up to 48 weeks of pegIFN and RBV was well tolerated and efficacious. The maximum decreases from baseline in $\log_{10}$ HCV RNA levels during DAA monotherapy treatment with any one of the DAAs were all statistically significantly greater than placebo ($P < 0.016$). Additionally, the SVR_{12} and SVR_{24} rates for all subjects who received one of the DAAs of ABT-450/r, ABT-072, or ABT-333 in combination with pegIFN and RBV were statistically significantly different from placebo with pegIFN and RBV ($P \leq 0.024$). In general, no clinically significant adverse effects were noted by the addition of ABT-450/r, ABT-333, or ABT-072 to a pegIFN/RBV regimen in HCV-infected subjects that would preclude continued evaluation of these agents. This study supports continued evaluation of these DAAs for the treatment of HCV.

Date of Report: 07Dec2012

Protocol Changes

The original protocol (dated 21 December 2009) was amended twice during the course of the study. All changes made to the original protocol and the amended protocol are described below; changes made to the study statistical analysis methods are described in Section 9.8.2.

Amendment No. 1

Amendment No. 1 was dated 12 February 2010. The purpose of this amendment was to:

- Allow liver biopsies to be performed during the screening period on any subject who met all inclusion and none of the exclusion criteria and had not had a liver biopsy within the past 3 years.
  Rationale: To include eligible subjects who might otherwise not be able to participate.
- Remove the Study Day 25 visit.
  Rationale: Procedures were combined with Study Week 4 visit to decrease visit burden on subjects and sites.
- Clarify that the Beck's Depression Index II (BDI-II) could not be retaken and if a subject scored > 21, they should have been screen failed.
  Rationale: To clarify that per instrument guidelines, the BDI-II may not be retaken and therefore, subjects with a BDI-II score > 21 may not be rescreened.
- Clarify the resistance monitoring visits for subjects who prematurely discontinued study drug treatment.
  Rationale: To clarify the visits and applicable procedures to be performed during this period for these subjects.
- Allow the subject to self-administer pegIFN on Study Days 18 and 25. However, if the subject chose to self-inject for these doses, the site was to contact the subject the next business day to ensure the dose was taken and record this in the subject's source.

Rationale: To allow subjects flexibility with the timing of their pegIFN injection.

- Clarify the visit windows allowed for Study Weeks 50, 52 and 56.
  Rationale: To clarify since the information was not included in the original protocol.
- Allow for documented prescription use of benzodiazepines and opiates and stable methadone therapy, however, the Sponsor medical monitor was to be contacted prior to subject enrollment.
  Rationale: To clarify the exclusionary medications.
- Clarify that subjects were prohibited from using CYP3A and CYP2C8 inhibitors or inducers from 1 month prior to and throughout DAA dosing.
  Rationale: These medications were only contraindicated while the subject was taking DAA.
- Modify Study Activities table (Table 4).
  Rationale: To update the table to reflect the changes in the protocol text.
- Remove cannabinoids from the urine drug screen.
  Rationale: To allow enrollment of subjects who have received marijuana for medical reasons where such use was permitted by law.
- Remove HAV IgM from screening labs.
  Rationale: Screening for acute hepatitis A was not warranted since it was not anticipated to occur with any frequency in the study population.
- Clarify the Study Drug Diary instructions.
  Rationale: To clarify the instructions for sites to give to subjects.
- Modify the dietary requirements while subjects were confined.
  Rationale: To be more in line with USDA guidelines.
- Clarify procedures/visits to be followed for subjects who prematurely discontinued study drug treatment.
  Rationale: To clarify for the sites the visits and procedures to be performed on subjects who prematurely discontinued study drug.

The protocol amendment was approved by the appropriate IECs/IRBs prior to implementation. The protocol with all changes incorporated and a detailed description of changes is presented in Appendix 16.1__1.

Amendment No. 2

Amendment No. 2 was dated 27 January 2011. The purpose of this amendment was to:

- Allow subjects randomized to an ABT-450/r treatment group, who had achieved RVR and remain virologically suppressed at all subsequent visits, the option of stopping pegIFN/RBV on or after Study Week 24.
  Rationale: There was recent evidence that subjects treated with other investigational HCV protease inhibitors in combination with pegIFN and RBV for a total of 24 weeks of therapy and who achieved extended RVR had a similar SVR rate compared to those subjects who received a total of 48 weeks of treatment. The option to stop pegIFN/RBV on or after Study Week 24 but before Week 48 therefore offered subjects the opportunity to decrease their exposure to pegIFN and RBV and their associated toxicities, without significantly impacting SVR. As there were no comparable data for subjects treated with non-nucleoside polymerase inhibitors, the option of response-guided shortening of pegIFN and RBV was not offered to those subjects who had been randomized to receive either ABT-333 or ABT-072.
- Clarify that subjects randomized to an ABT-450/r treatment group who were eligible and opted to stop pegIFN/RBV on or after Study Week 24 were not considered to have prematurely discontinued treatment.
  Rationale: Subjects who did not discontinue therapy due to virologic failure or adverse events, and who stopped therapy in accordance with the amended protocol, were presumed to have completed their protocol-specified course of treatment. Hence, their discontinuation was not defined as premature.
- Update Table 4 (Study Activities) with Post-Treatment Week 2 – Post-Treatment Week 24 visits.
  Rationale: All subjects were on the same schedule of events after pegIFN/RBV treatment had ended.

- Update Table 4 (Study Activities) to show that adverse events were to be collected at Post-Treatment Week 2 and Post-Treatment Week 4 visits (previously known as Study Weeks 50 and 52).
  Rationale: Updated to align with the Sponsor's internal policy regarding adverse event reporting.
- Added 2 columns (Post-Treatment Week 36 and Post-Treatment Week 48) to Table 4 (Study Activities).
  Rationale: Provide guidance in monitoring the development and persistence of antiviral resistance for 48 weeks in subjects who discontinued pegIFN/RBV treatment prior to Study Week 24.
- Clarify footnotes in Table 4 and the text to show that DAA assay samples or pegIFN/RBV assay samples should not be drawn after Study Week 12.
  Rationale: Subjects completed DAA treatment by Study Week 12; therefore, it was not possible to assay for the DAA after Study Week 12.
- Amend the text to indicate plasma samples were used for the Roche COBAS TaqMan® RT-PCR assay.
  Rationale: The central laboratory was scheduled to use plasma samples for this assay in this study.
- Provide end-of-treatment procedures for eligible ABT-450/r randomized subjects who opted to stop pegIFN/RBV on or after Study Week 24
  Rationale: To provide guidance for management of these subjects and to allow for monitoring of viral load and development of resistance.
- Update the text regarding discontinuation procedures for subjects who discontinued pegIFN/RBV after Study Week 12.
  Rationale: To clarify procedures for subjects who discontinued pegIFN/RBV after Study Week 12 and allowed for the monitoring of viral load and development of resistance.
- Delete the Discontinuation of Individual Subjects diagram since all subjects followed the same Post-Treatment schedule in the Study Activities Table, thereby reducing the number of visits.
  Rationale: Reduce the burden placed on subjects for monitoring visits and provide a consistent schedule of post-treatment follow-up for all subjects.

- Change the contact name from [redacted] to [redacted] (Section 9.5.4.3).
  Rationale: [redacted] *had replaced* [redacted] *in this role.*
- Amend the safety language in Section 9.5.1.8 regarding the collection of serious adverse events during the post-treatment period of the trial.
  Rationale: Updated to align with the Sponsor's internal policy regarding adverse event reporting.

The protocol amendment was approved by the appropriate IECs/IRBs prior to implementation. The protocol with all changes incorporated and a detailed description of changes is presented in Appendix 16.1__1.

List of Sites

Site Name/Post Office Address
Tulane University Health Sciences Center Department of Medicine Section of Gastroenterology SL 35 1430 Tulane Avenue New Orleans, LA 70112 United States
University of Utah Gastroenterology Division Health Sciences Center SOM 4R118 30 North 1900 East Salt Lake City, UT 84132-2410 United States
Orlando Immunology Center 1701 North Mills Avenue Orlando, FL 32803 United States
Advanced Clinical Research Institute Suite 303 1211 West La Palma Avenue Anaheim, CA 92801 United States
University of Colorado Denver Transplant Center & Hepatology Clinic B-154, AOP, Room 7085 1635 Aurora Court Aurora, CO 80045 United States
Gulf Coast Research, LLC Suite 180 7520 Perkins Road Baton Rouge, LA 70810 United States

Site Name/Post Office Address
Northwestern University Feinberg School of Medicine Division of Hepatology Suite 19-046 676 North St. Clair Street Chicago, IL 60611 United States
University of North Carolina at Chapel Hill Division of Gastroenterology and Hepatology Burnett Womack Bldg. CB# 7584 Manning Drive Chapel Hill, NC 27599-7584 United States
The Liver Institute at Methodist Dallas Pavilion III, Suite 268 1411 North Beckley Avenue Dallas, TX 75203 United States
Henry Ford Hospital 2799 West Grand Boulevard Detroit, MI 48202 United States
Weill Medical College of Cornell University Division of Gastroenterology and Hepatology 4th Floor 1305 York Avenue New York, NY 10021 United States
Virginia Mason Medical Center Center for Liver Disease Mailstop C3-GAS 1100 9th Avenue Seattle, WA 98101 United States
Indiana University IB327 975 West Walnut Street Indianapolis, IN 46202 United States

Site Name/Post Office Address
Alamo Medical Research Suite 202 621 Camden Street San Antonio, TX 78215 United States
University of Wisconsin Hospital and Clinics Section of Gastroenterology and Hepatology H6/516 – MC 5124 600 Highland Avenue Madison, WI 53792 United States
Orlando Clinical Research Center 5055 South Orange Avenue Orlando, FL 32809 United States
Duke Clinical Research Institute 2400 Pratt Street Durham, NC 27705 United States
Scripps Clinic Division of Gastroenterology/Hepatology 10666 North Torrey Pines Road/N203 La Jolla, CA 92037 United States
Cedars-Sinai Medical Center Hepatology Research Suite 430E 8631 West Third Street Los Angeles, CA 90048 United States

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NYU Langone Medical Center HCC, Suite 4J 530 First Avenue New York, NY 10016 United States
Minnesota Gastroenterology, PA Suite 423 South 2550 University Avenue West St. Paul, MN 55114 United States
Johns Hopkins University School of Medicine Viral Hepatitis Center Room 448 1830 East Monument Street Baltimore, MD 21287 United States
Mayo Clinic Hospital 5777 East Mayo Boulevard Phoenix, AZ 85054 United States
Advanced Liver Therapies St. Luke's Episcopal Hospital Baylor College of Medicine St. Luke's Episcopal Hospital Suite 1505 6620 Main Street Houston, TX 77030 United States