



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: ABT-450, ABT-072		
Name of Active Ingredient: (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> ,14,15,16,16 <i>a</i> -tetradecahydrocyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-14 <i>a</i> (5 <i>H</i>)-carboxamide hydrate (for ABT-450), Potassium 3-{3- <i>tert</i> -butyl-4-methoxy-5-[(<i>E</i>)-2-{4-[(methylsulfonyl)amino]phenyl}ethyl] phenyl}-2,6-dioxo-3,6-dihydro-2 <i>H</i> -pyrimidin-1-ide trihydrate (for ABT-072)		
Title of Study: An Open-Label Pilot Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of ABT-450 with Ritonavir (ABT-450/r) Dosed in Combination with ABT-072 and Ribavirin (RBV) in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection		
Coordinating Investigator: Eric Lawitz, MD		
Study Sites: Four investigative sites in the United States.		
Publications: Two abstracts		
Studied Period (Years): First Subject First Visit: 18 October 2010 Last Subject Last Visit: 03 April 2012	Phase of Development: 2a	



Objectives:

The primary objective of this study was to assess the safety, tolerability, and antiviral activity (percentage of subjects with HCV RNA < lower limit of quantitation [LLOQ; 25 IU/mL] from Week 4 through Week 12) of ABT-450/r administered in combination with ABT-072 and RBV under non-fasting conditions for 12 weeks in HCV genotype 1-infected treatment-naïve adults.

The secondary objectives of this study were to assess the following: pharmacokinetics of ABT-450/r and ABT-072 with RBV in HCV-infected subjects; percentage of subjects with HCV RNA < 1000 IU/mL at Study Week 2; percentage of subjects with HCV RNA < LLOQ at Study Week 4 of treatment; the time to failure to suppress or rebound in HCV RNA associated with this treatment regimen; time to relapse after the end of the treatment regimen; the percentage of subjects with SVR₁₂ (HCV RNA < lower limit of detection [LLOD; 15 IU/mL] 12 weeks post-DAA therapy), or SVR₂₄ (HCV RNA < LLOD 24 weeks post-DAA therapy); and the development and persistence of viral resistance with this treatment regimen.

Methodology:

This was a Phase 2a multicenter, open-label, single-arm, combination treatment study of a regimen of ABT-450/r, ABT-072, and RBV in HCV genotype 1 (1a or 1b) infected treatment-naïve adults. Only subjects with IL28B rs12979860 C/C genotype were enrolled. This study was designed to enroll up to 20 subjects, of which at least 10 subjects were to be infected with genotype 1a virus.

The study consisted of a screening phase, treatment, and post-treatment phase. The study included one treatment arm in which subjects received ABT-450/r 150/100 mg once daily (QD) dosed in combination with ABT-072 400 mg QD with weight-based RBV 1000 to 1200 mg orally (PO) divided twice daily. The treatment phase was no longer than 12 weeks.

Subjects who received at least one dose of DAA and who experienced virologic failure or relapse after therapy were offered pegIFN and RBV as standard of care (SOC) therapy for up to 48 weeks. SOC was to be started within 24 weeks of the end of DAA therapy and was not provided for subjects who were not viremic. The post-treatment phase was a follow-up phase during which subjects were monitored at regular intervals for sustained viral response for 24 weeks (SVR₂₄) and viral resistance through 48 weeks. Resistance monitoring was performed regardless of whether subjects received post-treatment SOC.

Number of Subjects (Planned and Analyzed):

Twenty subjects were planned. Eleven subjects were enrolled, dosed, and analyzed, as applicable.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV-infected, treatment-naïve adults 18 to 65 years of age, with a BMI of 18 to < 35. Females were either postmenopausal for at least 2 years or surgically sterile. Male subjects and/or partner(s) had to be practicing at least 1 effective method of birth control. Subjects were in a condition of general good health, other than the HCV infection. Subjects had a chronic HCV genotype 1 infection for at least 6 months prior to study enrollment with no evidence of cirrhosis, bridging fibrosis, or liver pathology due to any cause other than chronic HCV infection. Subjects had HCV RNA levels within the limits of detection at Screening and were IL28B rs12979860 genotype C/C. Subjects could not have previously received any investigational anti-HCV agents, interferon, pegIFN, or RBV.



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

The study drug regimens was ABT-450/r 150/100 mg QD, ABT-072 400 mg QD, 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 (bulk lot number 09-025889); coadministered ritonavir 100-mg soft gelatin capsules (bulk lot number 10-002930); ABT-072 50-mg tablet (bulk lot number 10-001331); and ABT-072 100-mg coated tablet (bulk lot number 10-003263).

RBV was provided as a 200-mg tablet (bulk lot number 10-002722) for oral administration.

Duration of Treatment:

Study drug (ABT-450/r, ABT-072, + RBV) was administered for up to 12 weeks.

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

Not applicable.

Criteria for Evaluation

Efficacy:

The primary efficacy endpoint was the simple percentage of all dosed subjects with HCV RNA suppressed below the LLOQ from Study Week 4 through Study Week 12. The secondary efficacy endpoints were: (1) the percentage of subjects with HCV RNA < 1000 IU/mL at Week 2, (2) the percentage of subjects with HCV RNA < LLOQ at Week 4, (3) the percentage of subjects with SVR₁₂ or SVR₂₄, (4) the time to failure to suppress or to rebound (confirmed increase of at least 0.5 log₁₀ IU/mL above nadir or confirmed HCV RNA > LLOD for subjects who previously achieved HCV RNA < LLOD) during treatment, and (5) the time to relapse after treatment (confirmed HCV RNA > LLOD). The resistance endpoints were: (1) the fold change from baseline and reference HCV samples in EC₅₀ at various time points, and (2) the identification of mutations at each amino acid position by nucleotide sequencing compared to baseline and prototypic sequences, and (3) to assess the development and persistence of viral resistance with this treatment regimen.

Pharmacokinetic:

Plasma concentrations for ABT-450, ABT-072, ritonavir, and ribavirin were summarized.

Safety:

Adverse events, clinical laboratory determinations, and vital signs were summarized and electrocardiograms were listed.



Statistical Methods

Efficacy:

The primary efficacy endpoint was the percentage of subjects with HCV RNA suppressed below the LLOQ from Week 4 through Week 12 out of all subjects dosed. A 95% binomial exact confidence interval for the percentage was supplied.

The secondary efficacy endpoints were as follows: percentage of subjects with HCV RNA < 1000 IU/mL at Week 2; the percentage of subjects with HCV RNA < LLOQ at Week 4; percentage of subjects with SVR₁₂ (HCV RNA < LLOD 12 weeks post-DAA therapy), or SVR₂₄ (HCV RNA < LLOD 24 weeks post-DAA therapy); time to failure to suppress or rebound (confirmed increase of at least 0.5 log₁₀ IU/mL above nadir or confirmed HCV RNA > LLOD for subjects who previously achieved HCV RNA < LLOD) during treatment; and time to relapse (defined as confirmed HCV RNA > LLOD) after treatment.

The percentage of subjects with HCV RNA < 1000 IU/mL at Week 2, and the percentage of subjects with HCV RNA < LLOQ at Week 4, and the percentage of subjects with SVR₁₂ and SVR₂₄ were presented with a 95% binomial exact confidence interval.

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

Samples through PT Week 24 were used for efficacy analysis. HCV RNA measurements after PT Week 24 were used only to determine which samples to evaluate for resistance.

The resistance endpoints were the fold change in EC₅₀ levels at each post-baseline time point compared to baseline and prototypic standards and the frequency of mutations at each amino acid position by nucleotide sequencing compared to baseline and prototypic standard sequences.

The development of resistance during treatment was assessed by calculating the fold change in EC₅₀ levels at each post-baseline time point compared both to baseline and prototypic standards. The fold changes at each time point were summarized.

The amino acid changes for population 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.

Pharmacokinetic:

Plasma concentrations of ABT-450, ritonavir, ABT-072 and ribavirin that were collected prior to dosing were tabulated for each subject from Day 1 through Week 12 and at any time after for each subsequent study visit. Summary statistics were computed for each sampling time.

To generate a plasma concentration time profile samples were binned per sampling time post-dose beginning with Week 3. Summary statistics were computed for each bin.



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 (version 14.1). The number and percentage of subjects having treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug) were tabulated by primary System Organ Class and MedDRA preferred term. The tabulation of the number of subjects with treatment-emergent adverse events also was provided with further breakdowns by severity rating and relationship to study drug. 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.

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 post-baseline visit were summarized. 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 post baseline 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 post baseline values meeting pre-specified Criteria for Potentially Clinically Significant Laboratory values were summarized.

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

Summary/Conclusions

Efficacy Results:

ABT-450/r, ABT-072, and RBV were administered for 12 weeks (Day 1 to Week 12; DAA treatment) and HCV RNA levels were monitored through 48 weeks post-DAA treatment. All 11 subjects completed 12 weeks of treatment and maintained HCV RNA levels < LLOQ from Week 4 through Week 12 of DAA treatment. Ten of 11 (90.9%) subjects achieved an SVR₂₄ (HCV RNA levels < LLOQ from end of DAA treatment through PT Week 24). The subject who did not achieve SVR₂₄, initiated treatment with pegIFN and RBV and had an HCV RNA level below 15 IU/mL at the last assessment. A second subject who achieved SVR₂₄ subsequently experienced virologic relapse, which was detected at PT Week 36. Thus a total of 2 subjects in this study experienced virologic relapse post-treatment.



Summary/Conclusions (Continued)

Efficacy Results (Continued):

Analysis of resistance data revealed that none of the 11 subjects had pre-existing NS3 variants at signature resistance-associated amino acid positions, whereas 1 subject had the NS5B variant Y448H present at baseline. Despite the presence of this variant in NS5B prior to treatment, the virus became undetectable in this subject at Week 4 and remained undetectable throughout the remainder of the study and for the entire 48 week post-treatment period. Another subject, subject, who experienced virologic relapse at PT Week 8, had the NS3 D168V variant but no resistance-associated amino acid variants in NS5B were present at the time of virologic failure. An additional subject, who met virologic relapse criteria at PT Week 36, had the resistance-associated variant Y448H present in NS5B but no variants were found in NS3. The presence of Y448H in NS5B at the time of virologic failure along with the fact that the NS3 and NS5B amino acid sequences in the sample taken at the failure time point were > 99% identical to the baseline sequences suggest that this late relapse was not due to a new infection.

Pharmacokinetic Results:

The steady state 20- to 24-hour post-dose concentration for ABT-450, ritonavir and ABT-072 are comparable to trough concentrations in healthy subjects when dosed with other DAAs. The steady state 8- to 12-hour post-dose concentration for ribavirin is comparable to trough concentrations in treatment-naïve HCV infected subjects when dosed with other DAAs and pegIFN.

Safety Results:

All 11 subjects received ABT-450/r 150/100 mg QD in combination with ABT-072 400 mg QD with weight-based RBV 1000 to 1200 mg PO divided twice daily for the duration of the 12-week DAA-treatment period with a mean (range) duration of treatment of 84.2 (84 to 85) days.

All subjects reported at least 1 treatment-emergent adverse event. Treatment-emergent adverse events occurring in 2 or more subjects were headache in 4 subjects, dry skin, fatigue, and nausea reported in 3 subjects each, and gastroesophageal reflux disease and rash in 2 subjects each. All treatment-emergent events were mild or moderate in severity; individual moderate events occurred in 1 subject each.

No subject experienced a treatment-emergent adverse event that was serious, or that resulted in death or discontinuation of study drug.

Mean changes from baseline for clinical laboratory were unremarkable for most parameters and potentially clinically significant laboratory values were infrequent, with a few exceptions.

Hematologic laboratory abnormalities that did occur with some frequency included decreases in hemoglobin, and hematocrit. Decreases from normal hemoglobin, hematocrit, and RBC values at baseline to an on-treatment value below the lower limit of normal occurred in approximately half of the subjects in this study and are well documented adverse effects associated treatment with RBV, which causes hemolytic anemia. No potentially clinically significant hematology values or adverse events associated with abnormal hematology values occurred during the study.



Summary/Conclusions (Continued)**Safety Results (Continued):**

For chemistry parameters, transient total and indirect hyperbilirubinemia during DAA treatment was observed in 3 of 11 subjects, with total bilirubin levels reaching the potentially clinically significant cutoff of $2 \times$ ULN in 2 subjects. These high total bilirubin values were predominantly due to increases in indirect bilirubin values. The absence of direct hyperbilirubinemia or associated increases in liver transaminases suggest that the transient hyperbilirubinemia observed in this study was mediated by inhibition of bilirubin transport rather than hepatic injury, which is consistent with the known inhibitory effect of ABT-450/r on the bilirubin transporter OATP1B1. The overall mean total and indirect bilirubin values increased from a baseline to a maximum value at Week 1 and gradually decreased during DAA treatment with Week 12 values remaining slightly above baseline; at PT Week 4, mean values were below baseline.

For ALT and AST, overall mean baseline values were at least $2 \times$ ULN for each parameter and, by Week 1, mean values had decreased to approximately the ULN and at subsequent visits mean values remained within normal limits for the duration of the treatment period. No individual liver enzyme (ALT, AST, alkaline phosphatase, or GGT) values met the protocol-specified potentially clinically significant criteria. One subject with preexisting diabetes mellitus and elevated glucose at baseline had a high glucose value that was considered a worsening of diabetes mellitus starting Day 1. No other subjects met a potentially clinically significant criterion for laboratory value and no other abnormal laboratory values were associated with an adverse event.

Changes from baseline for vital sign parameters were unremarkable and no vital sign values were associated with an adverse event.

Conclusions:

A 12-week regimen of ABT-450/r and ABT-072 with ribavirin was well tolerated and achieved HCV RNA suppression from Week 4 through Week 12 in 100% of non-cirrhotic, HCV genotype 1-infected subjects with IL28B CC genotype. Two subjects relapsed after the end of treatment, including one who relapsed after post-treatment Week 24. Nine of 11 subjects (82%) had HCV RNA levels $<$ LLOD at their last study visit (PT Week 48 for all subjects, except 1 subject lost to follow-up after PT Week 36). These results justify continued study of pegIFN-free, DAA-based regimens for the treatment of HCV genotype 1-infected patients.