

2.0 Synopsis

AbbVie GK	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: ABT-450, ritonavir, and ABT-267	Volume:	
Name of Active Ingredient: ABT-450: (2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)- <i>N</i> -(cyclopropylsulfonyl)-6-[[5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 atetradecahydrocyclopropa[<i>e</i>]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-14 <i>a</i> (5 <i>H</i>)-carboxamide hydrate ritonavir: 10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethylester, [5 <i>S</i> -(5 <i>R</i> *,8 <i>R</i> *,10 <i>R</i> *,11 <i>R</i> *)] 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	Page:	
Title of Study: A Phase 2 Study to Evaluate the Safety, Tolerability, Antiviral Activity, and Pharmacokinetics of ABT-450 with Ritonavir (ABT-450/r) and ABT-267 in Japanese Adults with Chronic Hepatitis C Virus Infection		
Coordinating Investigator: Fumitaka Suzuki, MD		
Study Sites: Eighteen investigative sites in Japan		
Publications: 1 abstract, 1 poster		
Studied Period (Years): First Subject First Visit: 24 July 2012 Last Subject Last Visit: 14 May 2014	Phase of Development: 2	

Objectives:

The primary objective of this study was:

- to evaluate the safety and antiviral activity (percentage of subjects achieving sustained virologic response 24 weeks post-dosing [SVR₂₄]) of ABT-450/r 150/100 mg + ABT-267 25 mg and ABT-450/r 100/100 mg + ABT-267 25 mg for 12 or 24 weeks within HCV genotype 1b and for 12 weeks in HCV genotype 2-infected Japanese adults.

The secondary objectives of this study were:

- to evaluate the percentage of subjects achieving sustained virologic response 12 weeks post-dosing (SVR₁₂) of ABT-450/r 150/100 mg + ABT-267 25 mg and ABT-450/r 100/100 mg + ABT-267 25 mg for 12 and 24 weeks in HCV genotype 1b-infected and for 12 weeks in genotype 2-infected Japanese adults;
- to evaluate end of treatment (EOT) response with ABT-450/r 150/100 mg + ABT-267 25 mg and ABT-450/r 100/100 mg + ABT-267 25 mg for 12 or 24 weeks within HCV genotype 1b and for 12 weeks in HCV genotype 2-infected Japanese adults.

Methodology:

This was a Phase 2a, multicenter, randomized, open-label, parallel-arm, combination treatment study exploring the antiviral activity, safety and pharmacokinetics of ABT-450/r and ABT-267 in HCV GT1b- and GT2-infected, pegIFN/RBV treatment-experienced Japanese adults.

This study consisted of two phases, the Treatment Phase and the Post-Treatment Phase. Subjects who completed both the Treatment and Post-Treatment Phase were in the study for a total of 60 or 72 weeks after enrollment.

The Treatment Phase was designed to explore the antiviral activity, safety, pharmacokinetics and dose ranging of ABT-450/r and ABT-267 for 12 or 24 weeks in Japanese subjects. The Post-Treatment Phase was designed to monitor and evaluate for the evolution and persistence of viral resistance to ABT-267 and ABT-450 in HCV GT1b- and GT2-infected Japanese subjects who had been exposed to ABT-267 and ABT-450/r.

The study consisted of two Cohorts that were enrolled in parallel. Cohort 1 was to include HCV GT1b-infected subjects only and Cohort 2 was to include HCV GT2-infected subjects only. Subjects in Cohort 1 were randomized 1:1:1:1 to four treatment arms (Arms 1 to 4), which enrolled null responders (at a minimum of 5 subjects per arm) and partial responders. Subjects in Cohort 2 were randomized 1:1 to two treatment arms (Arms 5 and 6), which enrolled null responders, partial responders, and relapsers.

The study treatments were as follows:

Cohort 1 (HCV GT1b)

- Arm 1: ABT-450/r 100/100 mg QD + ABT-267 25 mg QD for 12 weeks
- Arm 2: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD for 12 weeks
- Arm 3: ABT-450/r 100/100 mg QD + ABT-267 25 mg QD for 24 weeks
- Arm 4: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD for 24 weeks

Methodology (Continued):

Cohort 2 (HCV GT2)

Arm 5: ABT-450/r 100/100 mg QD + ABT-267 25 mg QD for 12 weeks

Arm 6: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD for 12 weeks

The primary analysis occurred after subjects completed the Post-Treatment Week 24 Visit or prematurely discontinued from the study. All subjects who received at least 1 dose of study drugs were to be monitored for safety, HCV RNA levels, and the emergence and/or persistence of resistant viral variants for an additional 48 weeks following the last dose of study drugs

Number of Subjects (Planned and Analyzed):

A minimum of 96 and a maximum of 120 subjects were planned to be enrolled; 110 subjects were enrolled (18 in Arm 1, 18 in Arm 2, 19 in Arm 3, 18 in Arm 4, 19 in Arm 5, and 18 in Arm 6), and all received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV GT1b- or GT2-infected Japanese males or females between the ages of 18 and 75 years, inclusive. Females were postmenopausal for at least 2 years, surgically sterile, or of childbearing potential and practicing 2 effective forms of birth control while receiving study drug. Males were surgically sterile or practicing 2 effective methods of birth control throughout the course of the study. All subjects had received prior treatment with pegIFN/RBV with response as follows:

Subjects were either:

- HCV GT1b-infected null responder or partial responder; or
- HCV GT2-infected null responder, partial responder or relapser.

Prior treatment response was defined as follows:

- Null responders: received at least 10 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a 2 log₁₀ IU/mL reduction in HCV RNA at Week 12 (acceptable range: between Weeks 10 – 16);
- Partial responders: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved 2 log₁₀ IU/mL reduction in HCV RNA at Week 12 (acceptable range: between Weeks 10 – 16), but failed to achieve HCV RNA undetectable (HCV RNA < LLOD) at the end of treatment;
- Relapsers: received at least one course of pegIFN/RBV for the treatment of HCV and HCV RNA was undetectable at the end of treatment, but HCV RNA was detectable within 24 weeks of treatment follow-up.

Subjects had chronic HCV GT1b or GT2 infection and plasma HCV RNA > 10,000 IU/mL at baseline.

Subjects also had absence of cirrhosis on the basis of documented results of liver biopsy within 24 months prior to or during screening (for example, a Metavir or New Inuyama fibrosis score 3 or an Ishak fibrosis score 4), or if no liver biopsy within 24 months prior to or during screening was available, any of the following: FibroTest[®] score 0.72 and aspartate aminotransferase (AST) to platelet ratio index (APRI) 2, FibroScan[®] result < 9.6 kPa; or a Discriminant Score (z) less than zero, according to the following formula:

$$z = 0.124 \times (\text{gamma-globulin (\%)}) + 0.001 \times (\text{hyaluronate}) (\mu\text{g l}(-1)) - 0.075 \times (\text{platelet} (\times 10(4) \text{ counts per mm}(3))) - 0.413 \times \text{gender (male, 1; female, 2)} - 2.005.$$

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

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
ABT-450	AbbVie	Oral	Tablet	50 mg	11-005848
Ritonavir	AbbVie	Oral	Capsule	100 mg	150082E ^a
ABT-267	AbbVie	Oral	Tablet	25 mg	11-002034

a. Vendor bulk lot number. AbbVie bulk lot number was 12-003312.

Duration of Treatment:

Subjects received ABT-450/r and ABT-267 for 12 weeks or 24 weeks.

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

Not applicable.

Criteria for Evaluation

Efficacy:

Virologic response was assessed by HCV RNA in log₁₀ IU/mL at various time points from Day 1 through 48 weeks after completion of treatment.

Resistance:

For subjects with virologic failure, the HCV amino acid sequence as determined by population nucleotide sequencing was compared with baseline and prototypic standard amino acid sequences.

Pharmacokinetic:

Individual plasma concentrations of ABT-450, ritonavir, and ABT-267 were tabulated and summarized.

Pharmacogenetic:

IL28B status (CC, CT, or TT) was determined for each subject and analyzed as a factor contributing to the subject's response to study treatment.

Safety:

Safety and tolerability were assessed throughout the study on the basis of adverse event monitoring and vital signs, physical examination, ECG, and laboratory tests assessments.

Statistical Methods

Efficacy, safety and demographic analyses were performed on all subjects who received at least one dose of study drug.

No data were to be imputed for any efficacy or safety analysis, except for all responder analyses of the percentage of subjects with undetectable/unquantifiable HCV RNA at a post-baseline visit. HCV RNA values were selected for analysis based on the defined visit windows. When there was no HCV RNA value in a defined visit window, the closest values before and after the window were used for flanking imputation, regardless of the value chosen for the subsequent and preceding window.

Efficacy:

The primary efficacy endpoint was as follows:

- The percentage of all dosed subjects with sustained virologic response 24 weeks post-dosing (SVR_{24actual}: HCV RNA < LLOQ 24 weeks after the last actual dose of study drug).

Statistical Methods (Continued)

Efficacy (Continued):

A 2-sided 95% binomial exact confidence interval for the percentage was supplied for each treatment arm. Within the genotype 1b cohort, the effects of treatment duration (12 weeks versus 24 weeks) and ABT-450 dose (100 mg versus 150 mg) were to be tested using a logistic regression model with baseline \log_{10} HCV RNA level, treatment duration, ABT-450 dose, and prior treatment response (null responder, partial responder) as predictors. The interaction of treatment duration and ABT-450 dose was to be assessed. If there was evidence of an interaction between treatment duration and ABT-450 dose, the effect of treatment duration was to be tested separately for the ABT-450 100 mg and 150 mg treatment regimens and the effect of ABT-450 dose was to be tested separately for 12-week and 24-week treatment regimens. Within the genotype 2 cohort, the effect of ABT-450 dose (100 mg versus 150 mg) was to be tested using a logistic regression model with baseline \log_{10} HCV RNA level, ABT-450 dose, and prior treatment response (null responder, partial responder, relapser) as predictors.

The secondary efficacy endpoints were as follows:

- The percentage of all dosed subjects with sustained virologic response 12 weeks post-dosing (SVR_{12actual}: HCV RNA < LLOQ 12 weeks after the last actual dose of study drug), and
- The percentage of subjects with Week 12/24 response (i.e., end of treatment response; HCV RNA < LLOQ at Week 12 for the 12-week duration arms and HCV RNA < LLOQ at Week 24 for the 24-week duration arms).

For each secondary endpoint, a 2-sided 95% binomial exact confidence interval for the percentage was supplied for each treatment arm. The effects of treatment duration and ABT-450 dose within the HCV GT1b cohort and the effect of ABT-450 dose within the HCV GT2 cohort was to be tested for the secondary efficacy endpoints as described for the primary efficacy endpoint.

Additional efficacy endpoints included percentages of subjects with rapid virologic response (HCV RNA < LLOQ at Week 4), unquantifiable HCV RNA level, SVR_{12actual}, SVR_{24actual}, failure to suppress or rebound, and relapse; time to suppression, relapse, and failure to suppress or rebound; and change from baseline in HCV RNA level. For each additional endpoint, except time to suppression of HCV RNA, time to relapse, time to failure to suppress or rebound during treatment, and the change from baseline in \log_{10} HCV RNA levels, a 2-sided 95% binomial exact confidence interval for the percentage was supplied for each treatment arm.

Pharmacokinetic:

The C_{max} , T_{max} , and AUC_{24} were determined using non-compartmental analyses and summarized after the first dose of ABT-450/r and ABT-267 on Treatment Study Day 1. Plasma concentrations of ABT-450, ABT-267, and ritonavir were tabulated for each subject and group.

Resistance:

For subjects with virologic failure, the HCV amino acid sequence as determined by population nucleotide sequencing was compared with baseline and prototypic standard amino acid sequences. The number of subjects whose amino acid sequence did not match that of either baseline or prototypic sequence at an amino acid position for each visit, out of the total number of subjects, was summarized. Summaries by treatment group (and accompanying listings) were created for all subjects who did not achieve SVR₂₄ to assess the effects of substitutions per population sequencing for each target gene on failure.

Statistical Methods (Continued)

Safety:

The number and percentage of subjects having treatment-emergent adverse events (TEAE, defined as any event that began or worsened in severity after initiation of study drug through 30 days post-study drug dosing) were tabulated by primary MedDRA System Organ Class and preferred term. Within the HCV GT1b cohort, comparisons of the percentages of subjects with treatment-emergent events between treatment durations and between ABT-450 doses were made using a Cochran-Mantel-Haenszel (CMH) test controlling for treatment duration and ABT-450 dose. Within the HCV GT2 cohort, percentages were compared between the ABT-450/r 100/100 mg + ABT-267 for 12 weeks and ABT-450/r 150/100 + ABT-267 for 12 weeks arms using Fisher's exact tests. The tabulation of the number of subjects with TEAEs also was provided with further breakdown by severity rating and relationship to study drug (ABT-450/r and/or ABT-267). 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.

Summary/Conclusions

Efficacy Results:

High SVR₂₄ rates were achieved in HCV GT1b-infected subjects treated with ABT-450/r (100 mg/100 mg or 150 mg/100 mg) QD + ABT-267 25 mg QD for 12 or 24 weeks. SVR₂₄ rates for subjects with HCV GT1b infection were 100% in Arms 1, 3, and 4 and 88.9% in Arm 2. Due to the very high SVR₂₄ rates achieved, no correlation with ABT-450 dose (150 mg versus 100 mg) was observed and no meaningful differences among subgroups could be determined. The 2 subjects with HCV GT1b infection who did not achieve SVR₂₄ failed to do so because of post-treatment relapse or premature study drug discontinuation due to a SAE. No HCV GT1b-infected subject relapsed after achieving SVR₂₄. SVR₂₄ rates were lower in subjects with HCV GT2 infection than in those with HCV GT1b infection. For subjects with HCV GT2 infection, a numerically higher, but not statistically significantly different, SVR₂₄ rate was achieved with ABT-450 150 mg (72.2%) than with ABT-450 100 mg (57.9%) when administered with ritonavir 100 mg + ABT-267 25 mg QD for 12 weeks. Among HCV GT2-infected subjects, the most common reason for not achieving SVR₂₄ was on-treatment virologic failure; the other reason for not achieving SVR₂₄ was post-treatment relapse. The proportions of subjects with HCV GT2 infection (Arms 5 and 6) who achieved SVR₂₄ was numerically higher in subjects with HCV GT2 subtype 2a (81.8% in Arm 5 and 100% in Arm 6) than in those with HCV GT2 subtype 2b (25.0% and 37.5%). Notably, among the 13 HCV GT2-infected subjects who did not achieve SVR₂₄, all but 2 were infected with HCV subtype 2b. No HCV GT2-infected subject relapsed after achieving SVR₂₄. Among subjects with HCV GT1b infection, all achieved EOT response and all but 2 achieved SVR₁₂. EOT response and SVR₁₂ rates were lower among subjects with HCV GT2 infection than among those with HCV GT1b infection. Among HCV GT2-infected subjects, EOT response and SVR₁₂ rates were numerically higher in the Arm that received ABT-450 150 mg (Arm 6) than in the Arm that received ABT-450 100 mg (Arm 5) (EOT response rate: 83.3% versus 63.2%; SVR₁₂ rate: 72.2% versus 57.9%). Outcomes for the additional efficacy endpoints, RVR and SVR₄, were consistent with those for the primary and secondary endpoints.

Summary/Conclusions (Continued)

Resistance Results:

Resistance analyses were conducted on baseline samples from all subjects, and on samples collected at the time of virologic failure from all subjects who experienced failure. There was no apparent association between the presence of variants at resistance-associated amino acid positions in NS3 or NS5A at baseline and treatment outcome in HCV GT1b- or HCV GT2-infected subjects in this study. The resistance-associated, treatment-emergent variants in HCV GT1b-infected subjects observed at the time of failure were D168V in NS3, and L28V, L31F and Y93H in NS5A. Most subjects with HCV GT2 who experienced virologic failure had a D168 variant in NS3, and L28F in NS5A, at the time of failure. While the NS3 variants in general did not persist to Post-Treatment Week 24, all of the NS5A variants were detected at Post-Treatment Week 24 and/or Post-Treatment Week 48.

Pharmacokinetic Results:

ABT-450 pharmacokinetics were nonlinear and increased supra-proportionally with dose when ABT-450 was coadministered with ritonavir and ABT-267 in HCV-infected, treatment-experienced Japanese subjects, consistent with the nonlinearity observed in healthy Japanese subjects and healthy or HCV-infected Western subjects. At the ABT-450/r 100/100 mg dose, the Day 1 ABT-450 geometric mean exposures (C_{max} and AUC) in HCV GT1b- and GT2-infected Japanese subjects were comparable. However at the ABT-450/r 150/100 mg dose, the Day 1 ABT-450 geometric mean exposures in HCV GT2-infected Japanese subjects were higher than those in HCV GT1b-infected Japanese subjects, which may be due to the high variability observed in the ABT-450 exposures. Similarly, regardless of ABT-450 dose, ABT-267 geometric mean Day 1 exposures were slightly higher in HCV GT2-infected Japanese subjects than in HCV GT1b-infected Japanese subjects. On the other hand, regardless of ABT-450 dose, ritonavir mean Day 1 exposures were comparable between HCV GT1b- and GT2-infected Japanese subjects.

Safety Results:

Among the 110 subjects in the safety population, 81.8% reported at least one TEAE and 40.0% reported at least one TEAE that was considered by the investigator to have a reasonable possibility of being related to study treatment. Overall, the frequency of TEAEs appeared to be similar with study treatment duration of 12 or 24 weeks, or with ABT-450 dose 100 mg or 150 mg. Maximum severity of TEAEs was mild in all subjects with the exception of 8 subjects in whom maximum severity of TEAEs was moderate and one subject in whom maximum severity of TEAEs was severe.

Summary/Conclusions (Continued)

Safety Results (Continued):

The most common TEAEs (10% of all subjects combined) were nasopharyngitis in 29.1% and headache in 13.6% of subjects. There were no overall trends in the frequencies of TEAEs with respect to treatment duration (12 weeks or 24 weeks) or ABT-450 dose (100 mg or 150 mg), but a few statistically significant differences were noted for certain TEAEs. These differences were not considered clinically meaningful, at least in part due to consideration of the small number of subjects observed. There was a higher frequency ($P = 0.008$) of nasopharyngitis in subjects who received ABT-450 150 mg (36.1% in Arm 2 + 6 or 50% of subjects in Arm 4) than in those who received ABT-450 100 mg (16.2% or 21.1%, respectively). Because a physiological explanation associating nasopharyngitis with ABT-450 dose is not readily apparent and subject numbers are small, this finding is not considered to be clinically meaningful. A statistical difference between subjects assigned to receive ABT-450 100 mg versus 150 mg was also noted for pyrexia ($P = 0.048$), however this event occurred with lower frequency in subjects who received the higher dose of ABT-450 (150 mg; 0% of subjects in Arm 2 + 6 or Arm 4) than in those who received ABT-450 100 mg (5.4% in Arm 1 + 5 or 10.5% in Arm 3). Because a physiological explanation associating pyrexia with ABT-450 dose is not apparent, pyrexia occurred at a higher rate with the lower ABT-450 dose, and subject numbers are small, this finding is not considered to be clinically meaningful. Rash occurred more often with a treatment duration of 24 weeks than with 12 weeks (10.5% in Arm 3 and 16.7% in Arm 4 versus 0% in Arm 1 or 2, $P = 0.024$) and the pattern for gastroenteritis was similar (10.5% in Arm 3 or 11.1% in Arm 4 versus 0% in Arm 1 or 2, $P = 0.045$). However, this is considered a sporadic finding not related to the duration of therapy because in subjects assigned to receive 24 weeks of study drug, the onset was within the first 12 weeks for most cases of rash or gastroenteritis.

One subject experienced a hepatotoxicity-related AE, autoimmune hepatitis, as identified with an SMQ (severe events only – broad search). This subject had a history of autoimmune hepatitis, completed study treatment, and achieved SVR₂₄. This subject was also the only subject who met the criteria to be evaluated by the Expert Hepatic Panel.

Two subjects experienced gall bladder-related AEs, as identified with an SMQ (narrow search).

One subject had a history of pre-existing gallbladder disease (polyp), a condition which is known to recur. Increasing age and female gender are known risk factors for cholelithiasis; both subjects were postmenopausal women and experienced cholelithiasis that was considered by the investigator to be mild and to have a reasonable possibility of being related to study treatment. These events were nonserious and did not result in study drug discontinuation.

The events identified with the drug-induced rash CMQ were considered by the investigator to be mild in severity, with the exception of a rash in a subject in Arm 4 (Subject █████) that was considered to be moderate in severity and possibly related to study treatment; all events identified with the drug-induced rash CMQ were nonserious and did not result in study drug discontinuation.

Serious adverse events occurred in 5 subjects during the study; the SAEs were autoimmune hepatitis, body fluid retention, femur fracture, tibia fracture, and ischemic colitis. Only the subject with fluid retention discontinued study treatment due to the AE.

Summary/Conclusions (Continued)

Safety Results (Continued):

In general, hematology, chemistry, urinalysis, immunology, and vital signs values did not vary with duration of treatment or ABT-450 dose. In the absence of RBV, reductions in hemoglobin from baseline to the Final Treatment Visit observed with the regimen of ABT-450/r and ABT-267 (2DAA) in Japanese subjects were similar to that observed with the regimen of ABT-450/r, ABT-267 and ABT-333 (3DAA) in Western subjects in Study M13-389 (-1.9 to -6.7 with 2DAA and -4.4 g/L with 3DAA). In particular, mean changes in hemoglobin level from baseline to Final Treatment Visit did not differ significantly between study treatment durations of 12 weeks versus 24 weeks in subjects with HCV GT1b infection, or between ABT-450 doses of 100 mg versus 150 mg in subjects with HCV GT1b or GT2 infection. Also of note, none of the patients received erythropoietin for their anemia, and the hematologic effects are noted to be lower than other DAAs like boceprevir and telaprevir.

Although not clinically relevant, mean change from baseline to the Final Treatment Visit in alkaline phosphatase was significantly greater with 24 weeks of treatment than with 12 weeks of treatment in the HCV GT1b Cohort, and was significantly greater with ABT-450 150 mg than with ABT-450 100 mg. However, mean change from baseline to Post-Treatment Week 4 in alkaline phosphatase did not differ significantly between subjects assigned to receive treatment durations of 12 or 24 weeks, or ABT-450 100 mg or 150 mg. In addition, although there were statistically significant differences between the ABT-450 doses and between the treatment durations in mean changes from baseline to the Final Treatment Visit for alkaline phosphatase values, the mean values within each group at the Final Treatment Visit were within the reference range. Only 1 subject met PCS criteria for alkaline phosphatase, this was an isolated (one-time) increase, and no subject had a grade 2 or higher value.

Potentially clinically significant values for calculated creatinine clearance and eGFR were observed more often in subjects who received 24 weeks of treatment than in those who received 12 weeks of treatment, but in subjects assigned to receive 24 weeks of treatment, the first instances of a confirmed PCS creatinine clearance or eGFR value occurred during the first 12 weeks of treatment in all subjects. Some subjects in whom the decrease was noted were receiving concomitant medications that have a known drug-drug interaction with ABT-450/r. Of note, subjects could be enrolled in Study M12-536 with a screening creatinine clearance value as low as 50 mL/min. Overall, the rates of PCS calculated creatinine clearance and PCS eGFR values were not considered to be related to the duration of treatment. No clinically relevant abnormalities in urinalysis, vital signs, or ECG results were observed.

No grade 3 or grade 4 clinical laboratory abnormalities in hemoglobin, alkaline phosphatase, or total bilirubin levels occurred during the study, and grade 3 abnormalities in ALT or AST occurred in one subject each. The subject who experienced a grade 3 ALT elevation was evaluated by an independent External Hepatic Panel. The subject did not meet biochemical criteria for Hy's Law, and the panel attributed a DILIN score of Unlikely for the subject, as the ALT elevation preceded study drug administration and persisted after study drug discontinuation, and the liver biopsy indicated autoimmune hepatitis (that may have been induced by prior IFN therapy). The Panel noted a possibility that the idiopathic autoimmune hepatitis was IFN-induced and stated that aggravation of the condition by study drug could not be ruled out.

A grade 2 increase in bilirubin level occurred in 2 subjects, but was not associated with increases in ALT or AST, and subsequently improved spontaneously in both subjects; there were no events of jaundice or scleral icterus in any subjects. The predominantly indirect hyperbilirubinemia and timing of the bilirubin elevations indicate that the elevations are likely a result of the OATP1B1 inhibition, which is known to occur with ABT-450. A grade 2 decrease in hemoglobin level occurred in one subject.

No subject died during the study.

Summary/Conclusions (Continued)

Conclusions:

In this Phase 2 study, high SVR₂₄ rates were observed in HCV GT1b-infected Japanese subjects, regardless of ABT-450 dose (100 or 150 mg) or treatment duration (12 or 24 weeks). SVR₂₄ rates in HCV GT1b-infected subjects were 100% in 3 treatment arms and 88.9% (16/18) in a fourth treatment arm. The 2 subjects with HCV GT1b infection who did not achieve SVR₂₄ failed to do so because of post-treatment relapse or premature study drug discontinuation due to a SAE. Given the high SVR₂₄ rates achieved in all HCV GT1b-infected cohorts, no meaningful differences could be discerned among subgroups.

SVR₂₄ rates were lower among cohorts of subjects with HCV GT2 infection than those with GT1b infection. For subjects with HCV GT2 infection, a numerically higher, but not statistically significantly different, SVR₂₄ rate was achieved with ABT-450 150 mg + ABT-267 25 mg QD for 12 weeks (72.2%) than with ABT-450 100 mg (57.9%) when administered with ritonavir 100 mg + ABT-267 25 mg QD for 12 weeks. The most common reasons HCV GT2-infected subjects did not achieve SVR₂₄ were on-treatment virologic failure and post-treatment relapse. Most subjects with HCV GT2 infection who did not achieve SVR₂₄ were infected with HCV subtype 2b. A numerically higher, but not statistically significantly higher, SVR₂₄ rate was observed in subjects with HCV GT2 subtype 2a (81.8% in Arm 5 and 100% in Arm 6) than in those with HCV GT2 subtype 2b (25.0% and 37.5%).

Agreement between SVR₁₂ and SVR₂₄ was 100% in all subjects, and no subject relapsed after achieving SVR₂₄.

The safety and tolerability of ABT-450/r 100/100 mg + ABT-267 or ABT-450 150/100 mg + ABT-267 administered for 12 weeks and of ABT-450/r 100/100 mg + ABT-267 or ABT-450 150 mg/100 mg + ABT-267 administered for 24 weeks appeared to be similar in HCV GT1b- and GT2-infected Japanese adults. In addition, rates of study drug discontinuation and SAEs were low, regardless of treatment duration (12 or 24 weeks) or ABT-150 dose (100 mg or 150 mg).

Overall, these results suggest that the combination regimen of ABT-450/r (100/100 mg or 150/100 mg) and ABT-267 (25 mg) provides safety and efficacy in this subject population and support further evaluation in Phase 3 studies.