

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: ABT-493 (glecaprevir)/ ABT-530 (pibrentasvir)		
Name of Active Ingredient: ABT-493/ABT-530		
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Treatment-Naïve and Treatment-Experienced, Non-Cirrhotic Asian Adults with Chronic Hepatitis C Virus Genotype (GT) 1 to GT6 Infection With or Without Human Immunodeficiency Virus Co-Infection (VOYAGE-1)		
Coordinating Investigator: ██████████		
Study Sites: 47 sites in China, South Korea, and Singapore		
Publications: 0		
Studied Period (Years): First Subject First Visit: 04 October 2017 Last Subject Last Visit: 15 February 2019	Phase of Development: 3	
Objectives: <p>The primary objectives of this study were to compare, among the combined group of genotype (GT) 1 – GT6-infected subjects, among the GT1-infected subjects, and among the GT2-infected subjects, the percentage of subjects achieving sustained virologic response 12 weeks postdosing (SVR₁₂) (hepatitis C virus [HCV] ribonucleic acid [RNA] < lower limit of quantification {LLOQ} 12 weeks after the last actual dose of study drug) to a historical SVR₁₂ rate and to assess the safety following 8 or 16 weeks of treatment with the ABT-493/ABT-530 combination regimen in treatment-naïve (TN) or treatment-experienced with regimens containing interferon (IFN) (alpha, beta, or pegylated interferon [pegIFN]) with or without ribavirin (RBV), or sofosbuvir (SOF) with RBV with or without IFN (TE-PRS), non-cirrhotic adults with chronic HCV GT1 – GT6 infection, and with or without human immunodeficiency virus (HIV) co-infection.</p> <p>The secondary objectives were to assess the percentage of subjects with on-treatment HCV virologic failure, the percentage of subjects with post-treatment (PT) relapse of HCV infection, and the percentage of HCV/HIV co-infected subjects achieving SVR₁₂.</p> <p>An additional objective was to assess pharmacokinetics of ABT-493 and ABT-530 in Asian HCV-infected adults.</p>		

Methodology:

This was a Phase 3, randomized, double-blind (DB), placebo-controlled, multicenter study evaluating the efficacy, safety, and pharmacokinetics of ABT-493/ABT-530 in non-cirrhotic chronic HCV GT1 – GT6-infected Asian adult subjects with or without HIV co-infection who were HCV TN or TE-PRS.

Eligible HCV GT1 – GT6-infected non-cirrhotic subjects were randomized to Arm A or Arm B (defined below) in the following ratios: China: 2:1 for GT1, 2:1 for GT2, and 2:1 for combined GT3 – 6; South Korea and Singapore: 2:1 for GT1 and 2:1 for GT2.

- Arm A: ABT-493/ABT-530 300 mg/120 mg once daily (QD) for 8 weeks or 16 weeks
- Arm B: Matching placebo for 8 or 16 weeks followed by open-label (OL) ABT-493/ABT-530 300 mg/120 mg QD for 8 or 16 weeks

Subjects who were randomized to Arm B received OL ABT-493/ABT-530 300 mg/120 mg QD for 8 or 16 weeks following the DB Treatment Period.

Treatment duration in both the DB and OL Treatment Periods differed among subjects based on HCV genotype and treatment experience (8 weeks of treatment for GT1-, 2-, 3-, 4-, 5-, and 6-infected subjects with the exception of 16 weeks for TE-PRS GT3-infected subjects).

Safety and efficacy were assessed by AbbVie throughout the study.

In the PT Period, all subjects administered at least 1 dose of active study drug were followed for 24 weeks following the last dose of active study drug to monitor for safety, HCV RNA, the emergence and/or persistence of resistance-associated viral variants, plasma HIV-1 RNA, and HIV resistance.

Number of Subjects (Planned and Analyzed):

Planned: approximately 504 subjects.

Analyzed: 545 subjects were enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria:

- Male or female of Asian descent at least 18 years of age at time of screening
- If female, either postmenopausal or permanently surgically sterile, or women of child-bearing potential practicing at least 1 protocol-specified method of birth control on or prior to Study Day 1 through at least 30 days after the last dose of study drug.
- Screening laboratory result indicating HCV GT1, 2, 3, 4, 5 or 6-infection.
- Subject had positive HCV antibody (Ab) and plasma HCV RNA viral load \geq 1000 IU/mL at screening visit.
- Chronic HCV infection, defined as 1 of the following:
 - Positive for anti-HCV antibody or HCV RNA at least 6 months before screening, or
 - A liver biopsy consistent with chronic HCV infection.
- HCV TN (had never received any approved or investigational HCV treatment) or TE-PRS. Previous HCV treatment must have been completed \geq 8 weeks prior to screening.

Diagnosis and Main Criteria for Inclusion (Continued):

- Documented as noncirrhotic defined as meeting one of the following criteria:
 - A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis (e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of ≤ 3 , Ishak fibrosis score of ≤ 4); or
 - A FibroScan[®] score of < 12.5 kPa within 6 months of screening or during the screening period; or
 - Subjects with indeterminate FibroScan[®] score ($12.5 \leq \text{score} < 14.6$), must have had a qualifying liver biopsy.
 - A screening FibroTest score of ≤ 0.48 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) < 1 .
 - Subjects with indeterminate FibroTest ($0.48 < \text{result} < 0.75$), or conflicting FibroTest and APRI results must have had a qualifying liver FibroScan[®] or biopsy.

Main Exclusion Criteria:

- Female who was pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
- Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could have precluded adherence to the protocol, in the opinion of the investigator.
- Positive test result at screening for hepatitis B surface antigen (HBsAg) or hepatitis B virus deoxyribonucleic acid (DNA) was detectable if HBsAg was negative.
- HCV genotyping performed during screening indicated coinfection with more than 1 HCV genotype.
- Any cause of liver disease other than chronic HCV infection.
- Any current or past clinical evidence of decompensated liver disease such as ascites noted on physical exam, use of diuretics for ascites, hepatic encephalopathy, or esophageal variceal bleeding.
- Consideration by the investigator, for any reason, that the subject was an unsuitable candidate to receive ABT-493/ABT-530.
- History of severe, life-threatening or other significant sensitivity to any excipients of the study drug.

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

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
ABT-493/ABT-530	AbbVie	Oral	Film-coated tablet	100 mg/40 mg	16-005216
Placebo for ABT-493/ABT-530	AbbVie	Oral	Film-coated tablet	0 mg	15-005142 17-004336

Duration of Treatment:

Arm A subjects received ABT-493/ABT-530 300 mg/120 mg QD for 8 or 16 weeks.

Arm B subjects received matching placebo for 8 or 16 weeks followed by OL ABT-493/ABT-530 300 mg/120 mg QD for 8 or 16 weeks

Criteria for Evaluation

Efficacy:

Virologic response was assessed by plasma HCV RNA levels in IU/mL at various time points from Day 1 through 24 weeks after completion or discontinuation of active treatment in either the DB Treatment Period (Arm A) or the OL Treatment Period (Arm B).

Resistance:

For all subjects enrolled in South Korea or Singapore who received active study drug and experienced virologic failure, the HCV amino acid variants at signature resistance-associated amino acid positions in nonstructural viral protein 3 (NS3) and nonstructural viral protein 5A (NS5A) at baseline identified by next-generation sequencing (NGS) and comparison to the appropriate subtype-specific reference sequence were analyzed. For GT1-infected subjects who enrolled in China, received active study drug, and experienced virologic failure, the HCV amino acid variants at signature resistance-associated amino acid positions in NS3 and NS5A at baseline identified by population sequencing and comparison to the appropriate subtype-specific reference sequence were analyzed. In China, validated sequence analysis was available only for GT1.

The following resistance information was analyzed for subjects who received ABT-493/ABT-530, who experienced virologic failure, and who had an available postbaseline sample with HCV RNA ≥ 1000 IU/mL: 1) the amino acid substitutions in available postbaseline samples based on comparison to the baseline sequence, 2) the amino acid substitutions in available postbaseline samples at signature resistance-associated positions based on comparison to the appropriate subtype-specific reference sequence, and 3) the persistence of viral resistance.

Pharmacokinetic:

Individual plasma concentrations of ABT-493 and ABT-530 were tabulated and summarized for each subject, by visit, by subject's virologic failure status, and for all subjects combined.

Safety:

Safety and tolerability were assessed by monitoring adverse events (AEs), physical examinations, clinical laboratory tests, 12-lead electrocardiograms, and vital signs.

Statistical Methods

Efficacy:

The primary efficacy endpoint variable was SVR₁₂ for the subjects in the intention-to-treat (ITT) population treated with ABT-493/ABT-530 in the DB Treatment Period (Arm A). In order to control the Type I error rate, a fixed sequence testing procedure was used for the ranked primary efficacy endpoints. Only if success had been demonstrated for the first primary endpoint was testing to proceed to the second primary endpoint. Similarly, only if success had been demonstrated for the second primary endpoint was testing to proceed to the third primary endpoint.

The 3 ranked primary efficacy endpoints were:

1. The percentage of Arm A subjects from the combined group of GT1 – GT6-infected subjects who achieved SVR₁₂. The percentage of these subjects with SVR₁₂ was non-inferior to the historical SVR₁₂ rate of 96% if the lower confidence bound (LCB) of the 2-sided 95% confidence interval (CI) for the percentage was > 90%.
2. The percentage of Arm A subjects from the group of GT1-infected subjects who achieved SVR₁₂. The percentage of these subjects with SVR₁₂ was non-inferior to the historical SVR₁₂ rate of 97% if the LCB of the 2-sided 95% CI for the percentage was > 91%.
3. The percentage of Arm A subjects from the group of GT2-infected subjects who achieved SVR₁₂. The percentage of these subjects with SVR₁₂ was non-inferior to the historical SVR₁₂ rate of 95% if the LCB of the 2-sided 95% CI for the percentage was > 89%.

The normal approximation to the binomial distribution was used to calculate each CI unless the rate was 100%, in which case the Wilson score method was to be used for the calculation of the CI.

The secondary efficacy endpoints were:

- the percentage of Arm A subjects with on-treatment virologic failure (defined as confirmed increase of > 1 log₁₀ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment), and
- the percentage of Arm A subjects with PT relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment, excluding reinfection), and
- the percentage of Arm A HCV/HIV co-infected subjects (determined at screening) who achieved SVR₁₂.

For the analysis of relapse, a subject enrolled to receive 8 weeks of treatment was considered to have completed treatment if study drug duration was 52 days or more, and a subject enrolled to receive 16 weeks of treatment was considered to have completed treatment if study drug duration was 105 days or more.

The percentages of subjects with on-treatment HCV virologic failure, PT relapse, and SVR₁₂ were calculated along with 2-sided 95% Wilson score CIs.

In addition, a summary of reason for SVR₁₂ non-response (e.g., on-treatment virologic failure, relapse, re-infection) was provided for the set of all Arm A subjects and was to be provided for the set of HCV/HIV co-infected Arm A subjects.

The secondary endpoints were summarized for the set of all Arm A subjects in the ITT population and for the Arm A subjects in each of the GT1-infected and GT2-infected groups.

Statistical Methods (Continued)

Subgroup:

The percentage of subjects with SVR₁₂ was calculated, along with the corresponding 2-sided 95% Wilson score CIs, for the set of all Arm A subjects in the ITT population and for each of the GT1-infected and GT2-infected groups for subgroups such as geographic region, prior HCV treatment history, type of previous regimen for TE-PRS subjects, interleukin 28B (IL28B) genotype, and baseline HCV RNA level.

Resistance:

For subjects who enrolled in South Korea or Singapore: The genes of interest for NGS were those encoding full length nonstructural viral protein 3/4A (NS3/4A) and NS5A. The following resistance analyses were conducted: 1) baseline polymorphisms at signature amino acid positions (as well as a key subset of amino acid positions) at baseline identified by NGS at 2% or 15% detection thresholds were compared to the appropriate prototypic reference sequence and 2) a comparison of sustained virologic response rates for subjects with and without baseline variants at the positions of interest in NS3 and NS5A was provided. For subjects experiencing virologic failure, sequences at available postbaseline time points were compared to baseline and appropriate prototypic reference sequences to identify treatment-emergent substitutions.

For GT1-infected subjects who enrolled in China and experienced virologic failure: The genes of interest for population sequencing were those encoding amino acids 1-181 in NS3 and 1-251 in NS5A. For subjects experiencing virologic failure, sequences at available postbaseline time points were compared to baseline and appropriate prototypic reference sequences to identify treatment-emergent substitutions.

HCV Genotype/Subtype:

For subjects enrolled in South Korea and Singapore, phylogenetic analysis was conducted on all available HCV sequences from baseline samples in order to accurately determine HCV subtype.

Pharmacokinetic:

Individual plasma concentrations and pharmacokinetic parameter values for ABT-493 and ABT-530 were tabulated and summarized for each subject, by visit, by subject's virologic failure status, and for all subjects combined.

Safety:

All subjects who received at least 1 dose of study drug were included in the safety analyses. Safety data were summarized for the set of all subjects and separately for the geographic region of China. For safety analyses, data from the active (Arm A) and placebo (Arm B) treatment arms during the DB Treatment Period were summarized and comparisons between Arms A and B were performed, as appropriate, and data from Arm B during the OL Treatment Period were summarized separately with no comparisons performed.

For the active treatment arm during the DB Treatment Period (Arm A) and the active treatment arm during the OL Treatment Period (Arm B), treatment-emergent AEs were defined as any event that began or worsened in severity after initiation of active study drug through 30 days after the last dose of active study drug. For the placebo arm (Arm B), treatment-emergent AEs during the DB Treatment Period were defined as any event that began or worsened in severity after initiation of placebo through 30 days after the last dose of placebo and prior to OL Day 1 (if applicable).

Statistical Methods (Continued)

Safety (Continued):

The number and percentage of subjects with treatment-emergent AEs were tabulated by primary Medical Dictionary for Regulatory Activities (MedDRA[®]) system organ class and preferred term and the between-arm risk differences were calculated. Tabulations of the number of subjects with treatment-emergent AEs by severity grade (Grades 1 – 5) and relationship to study drug were also provided.

Mean changes in clinical laboratory and vital sign data from baseline to each post-baseline visit, including applicable PT visits, were summarized, and the differences between the active and placebo arms in the DB Treatment Period were analyzed using an ANOVA model with treatment arm as the factor. The number and percentage of subjects with post-baseline laboratory values during the Treatment Period (DB or OL) meeting toxicity grades were summarized, as were subjects meeting criteria for assessment of hepatic laboratory values. The number and percentage of subjects with post-baseline vital sign values during the Treatment Period (DB or OL) meeting pre-specified criteria for potentially clinically significant values were summarized by treatment arm.

Summary/Conclusions

Efficacy Results:

A total of 546 subjects were randomized and 545 subjects received at least 1 dose of study drug (ABT-493/ABT-530: n = 362; placebo n = 183). In China, 390 subjects were randomized and 389 subjects received at least 1 dose of study drug (ABT-493/ABT-530: n = 259; placebo n = 130).

The 3 ranked primary efficacy endpoints were achieved:

1. In Arm A, SVR₁₂ was achieved by 97.2% (352/362) in the combined group of GT1 – GT6-infected subjects, with a 2-sided 95% CI of 95.5% to 98.9% (data provided on next page). The LCB was above the 90% non-inferiority threshold. Therefore, the first of the 3 ranked primary SVR₁₂ endpoints was achieved, and ABT-493/ABT-530 demonstrated non-inferiority to the historical SVR₁₂ rate of 96% for pangenotypic treatment of HCV.
2. In Arm A, SVR₁₂ was achieved by 99.4% (178/179) in the group of GT1-infected subjects, with a 2-sided 95% CI of 98.3% to 100.0%. The LCB was above the 91% non-inferiority threshold. Therefore, the second of the 3 ranked primary SVR₁₂ endpoints was achieved, and ABT-493/ABT-530 demonstrated non-inferiority to the historical SVR₁₂ rate of 97% for treatment of HCV GT1 infection.
3. In Arm A, SVR₁₂ was achieved by 97.8% (136/139) in the group of GT2-infected subjects, with a 2-sided 95% CI of 95.4% to 100.0%. The LCB was above the 89% non-inferiority threshold. Therefore, the third of the 3 ranked primary SVR₁₂ endpoints was achieved, and ABT-493/ABT-530 demonstrated non-inferiority to the historical SVR₁₂ rate of 95% for treatment of HCV GT2 infection.

Two subjects in Arm A (2/362, 0.6%; 2-sided 95% CI: 0.2%, 2.0%), both in China, experienced on-treatment virologic failure. Six subjects in Arm A (6/359, 1.7%; 2-sided 95% CI: 0.8%, 3.6%), all in China, experienced Relapse₁₂.

Summary/Conclusions (Continued)			
Primary Efficacy Ranked Endpoints: Virologic Response at Post-Treatment Week 12 (SVR₁₂) in Arm A (ITT Population – Imputation of Missing Data as Failures)			
Assessment	Endpoint No. 1 GT1 – GT6- Infected Subjects Combined	Endpoint No. 2 GT1-Infected Subjects	Endpoint No. 3 GT2-Infected Subjects
SVR ₁₂ , n/N (%)	352/362 (97.2)	178/179 (99.4)	136/139 (97.8)
2-sided 95% CI ^a	95.5, 98.9	98.3, 100.0	95.4, 100.0
Nonresponse, n/N (%)	10/362 (2.8)	1/179 (0.6)	3/139 (2.2)
Reason for nonresponse, n/N (%)			
Virologic failure	8/362 (2.2)	0/179	2/139 (1.4)
On-treatment virologic failure	2/362 (0.6)	0/179	0/139
Breakthrough	2/362 (0.6)	0/179	0/139
End-of-treatment failure	0/362	0/179	0/139
Relapse ₁₂	6/359 (1.7)	0/178	2/139 (1.4)
Non-virologic failure	2/362 (0.6)	1/179 (0.6)	1/139 (0.7)
Premature study drug discontinuation	1/362 (0.3)	1/179 (0.6)	0/139
HCV reinfection ^b	0/362	0/179	0/139
Missing SVR ₁₂ data	1/362 (0.3)	0/179	1/139 (0.7)
Other	0/362	0/179	0/139
Threshold based on historic SVR ₁₂ rates			
Noninferiority threshold	90%	91%	89%
CI = confidence interval; GT = genotype; HCV = hepatitis C virus; IFN = interferon; ITT = intention-to-treat; QD = once daily; RBV = ribavirin; Relapse ₁₂ = virologic relapse by Post-Treatment Week 12; RNA = ribonucleic acid; SOF = sofosbuvir; SVR = sustained virologic response; SVR ₁₂ = sustained virologic response 12 weeks postdosing; TE-PRS = treatment-experienced with IFN (alpha, beta, or pegIFN) with or without RBV, or SOF with RBV with or without IFN			
a. Calculated using the normal approximation to the binomial distribution.			
b. Based on repeat genotype/subtype by central laboratory.			
Arm A: ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks or 16 weeks.			
Note: GT3 TE-PRS subjects received 16 weeks of treatment in each treatment period, as applicable; other subjects received 8 weeks of treatment.			
Other Notes: Backward imputation, where applicable, was used to impute missing data. After applying backward imputation, if there was still no value in the window but there was an HCV RNA from a local laboratory present, then it was to be imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.			

Summary/Conclusions (Continued)			
Among subjects enrolled in China and randomized to Arm A, SVR ₁₂ was achieved in 96.9% in the combined group of GT1 – GT6-infected subjects, 100% in the GT1-infected subjects, and 98.1% in the GT2-infected subjects.			
Virologic Response (SVR₁₂) Among Arm A Subjects in China (ITT Population – Imputation of Missing Data as Failures)			
Assessment	GT1 – GT6- Infected Subjects Combined	GT1-Infected Subjects	GT2-Infected Subjects
SVR ₁₂ , n/N (%)	251/259 (96.9)	110/110 (100)	103/105 (98.1)
2-sided 95% CI ^a	94.0, 98.4	96.6, 100.0	93.3, 99.5
Nonresponse, n/N (%)	8/259 (3.1)	0/110	2/105 (1.9)
Reason for nonresponse, n/N (%):			
Virologic failure	8/259 (3.1)	0/110	2/105 (1.9)
On-treatment virologic failure	2/259 (0.8)	0/110	0/105
Breakthrough	2/259 (0.8)	0/110	0/105
End-of-treatment failure	0/259	0/110	0/105
Relapse ₁₂	6/257 (2.3)	0/110	2/105 (1.9)
Non-virologic failure	0/259	0/110	0/105
Premature study drug discontinuation	0/259	0/110	0/105
HCV reinfection ^b	0/259	0/110	0/105
Missing SVR ₁₂ data	0/259	0/110	0/105
Other	0/259	0/110	0/105
CI = confidence interval; GT = genotype; HCV = hepatitis C virus; IFN = interferon; ITT = intention-to-treat; pegIFN = pegylated interferon; QD = once daily; RBV = ribavirin; Relapse ₁₂ = virologic relapse by Post-Treatment Week 12; RNA = ribonucleic acid; SOF = sofosbuvir; SVR = sustained virologic response; SVR ₁₂ = sustained virologic response 12 weeks postdosing; TE-PRS = treatment-experienced with IFN (alpha, beta, or pegIFN) with or without RBV, or SOF with RBV with or without IFN			
a. Calculated using the Wilson score method.			
b. Based on repeat genotype/subtype by central laboratory.			
Arm A: ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks or 16 weeks.			
Note: GT3 TE-PRS subjects received 16 weeks of treatment in each treatment period, as applicable; other subjects received 8 weeks of treatment.			
Other Notes: Backward imputation, where applicable, was used to impute missing data. After applying backward imputation, if there was still no value in the window but there was an HCV RNA from a local laboratory present, then it was to be imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.			

Summary/Conclusions (Continued)

Among Arm A subjects, sustained virologic response at 24 weeks postdosing (SVR₂₄) was achieved by 97.0% (351/362) in the combined group of GT1 – GT6 infected subjects and by 96.5% (250/259) of those from China. Agreement between SVR₁₂ and SVR₂₄ was 99.7% and 99.6% for the overall and China groups, respectively. Of those subjects in Arm A who achieved SVR₁₂, none relapsed during the SVR₂₄ window (Relapse₂₄).

For the Arm B subjects treated with ABT-493/ABT-530 300 mg/120 mg QD during the OL Treatment Period, SVR₁₂ was achieved by 97.3% (177/182) in the combined group of GT1 – GT6-infected subjects and by 96.9% (126/130) of those from China.

During the OL Treatment Period, 2 subjects in Arm B (2/182, 1.1%; 2-sided 95% CI: 0.3%, 3.9%), both in China, experienced on-treatment virologic failure. Three subjects in Arm B (3/180, 1.7%; 2-sided CI: 0.6%, 4.8%), 2 in China and 1 in South Korea, experienced Relapse₁₂.

Among Arm B subjects, SVR₂₄ was achieved by 96.2% (175/182) in the combined group of GT1 – GT6-infected subjects and by 96.2% (125/130) of those from China. Agreement between SVR₁₂ and SVR₂₄ was 98.9% and 99.2% for the overall and China groups, respectively. Of those subjects in Arm B who achieved SVR₁₂, none experienced Relapse₂₄.

Resistance Results:

Based on phylogenetic analysis of NS3/4A or NS5A sequences from 102 subjects enrolled in South Korea and Singapore, 3 GT1 and 2 GT2 subtypes were identified in the study, including 16 GT1a, 51 GT1b, 1 GT1c, 31 GT2a, and 3 GT2b-infected subjects. For Arm B subjects with available sequence, the number of subjects infected with each of the following HCV subtypes was: 6 GT1a, 28 GT1b, and 16 GT2a.

Among subjects enrolled in South Korea and Singapore, baseline polymorphisms at the key subset of amino acid positions in NS3 (positions 155, 156, or 168) were not detected in GT1-infected subjects in Arm A (0/67) or Arm B (0/34); and were detected in 5.9% (2/34) and (0/16) of the GT2-infected subjects in Arm A and Arm B, respectively; 2 GT2a-infected subjects had D168E in NS3. Baseline NS5A polymorphisms (at positions 24, 28, 30, 31, 58, 92, or 93) were detected in 40.9% (27/66) and 94.1% (32/34) of the GT1- and GT2-infected subjects, respectively, in Arm A; and 44.1% (15/34) and 93.8% (15/16) of the GT1- and GT2-infected subjects, respectively, in Arm B. Of note, Y93H was detected in 17.6% (9/51) and 10.7% (3/28) of the GT1b-infected subjects in Arm A and Arm B, respectively. The high prevalence of NS5A polymorphisms in GT2 was due to the common L/M31 polymorphism.

None of the subjects enrolled in South Korea or Singapore experienced virologic failure in Arm A and only 1 GT2a-infected subject in Arm B experienced virologic failure, indicating that baseline polymorphisms had no impact on treatment outcome in GT1- and GT2-infected subjects. The GT2a-infected subject experiencing virologic failure did not have baseline or treatment-emergent substitutions in NS3, and had the common GT2a polymorphism NS5A-L31M at baseline, and treatment-emergent substitution C92S in NS5A at the time of failure.

Pharmacokinetic Results:

Following administration of ABT-493/ABT-530 300 mg/120 mg in non-cirrhotic Asian adults with chronic HCV GT1 – GT6 infection, ABT-493 and ABT-530 concentrations quickly increased post-dose to the maximum level by approximately 2 to 4 hours. Steady-state plasma concentrations were attained by Day 7, and there was minimal drug accumulation for ABT-493 and ABT-530.

Summary/Conclusions (Continued)

Safety Results:

The fixed-dose combination of ABT-493/ABT-530 300 mg/120 mg QD administered for 8 weeks or 16 weeks (the latter for GT3 TE-PRS subjects) was well tolerated and demonstrated a favorable safety profile in HCV GT1 – GT6-infected subjects without cirrhosis, similar to the profile observed in subjects receiving placebo. The majority of subjects who experienced AEs in the ABT-493/ABT-530 arm during the DB Treatment Period or OL Treatment Period had events with a maximum severity of Grade 1 (mild), with the most common ($\geq 5.0\%$ of subjects) being upper respiratory tract infection. No significant differences in the incidence of AEs considered related to DAAs were observed between Arm A and Arm B (placebo) in the DB Treatment Period.

Serious AEs were rare (occurring in 0.8% of subjects in the ABT-493/ABT-530 arm during the DB Treatment Period and 2.7% during the OL Treatment Period), and none were related to study drug. No subject died during the study. No subject had an AE that led to premature discontinuation or interruption of study drug during the DB or OL Treatment Period. No subject experienced drug-induced liver injury or hepatic decompensation during the DB or OL Treatment Period.

Overall Conclusions:

- In chronic HCV GT1 – GT6-infected Asian subjects without cirrhosis, an 8- or 16-week regimen of ABT-493/ABT-530 300 mg/120 mg QD achieved a high rate of efficacy and was non-inferior to historical controls, meeting all 3 primary endpoints of the study:
 - SVR₁₂ achieved by 97.2% in the combined group of GT1 – GT6 infected Arm A subjects
 - SVR₁₂ achieved by 99.4% in the group of GT1-infected Arm A subjects
 - SVR₁₂ achieved by 97.8% in the group of GT2-infected Arm A subjects
- For Arm B subjects treated with ABT-493/ABT-530 300 mg/120 mg QD during the OL Treatment Period, SVR₁₂ was achieved by 97.3% (177/182) of subjects.
- The Relapse₁₂ rate was 1.7% in both Arm A (DB) and Arm B (OL). No subjects relapsed after achieving SVR₁₂.
- High SVR₁₂ rates were observed; however, the SVR₁₂ rate was numerically lower in the small number of subjects infected with GT3b (Arm A: 58.3%, 7/12; Arm B: 57.1%, 4/7), all of whom were from China. Most of the GT3b-infected subjects who did not achieve SVR₁₂ had a history of injection drug use and had baseline HCV RNA level $\geq 6,000,000$ IU/mL.
- Based on available data for Arm A and Arm B, baseline polymorphisms in NS3 and/or NS5A had no effect on treatment outcome in GT1 and GT2-infected subjects.
- In Arm A (DB) and Arm B (OL), ABT-493 and ABT-530 plasma concentrations quickly increased post-dose to the maximum level by approximately 2 to 4 hours. Steady-state plasma concentrations were attained by Day 7, and there was minimal drug accumulation for ABT-493 and ABT-530.
- The fixed-dose combination of ABT-493/ABT-530 300 mg/120 mg QD was well tolerated and demonstrated a favorable safety profile similar to placebo.