

## 2.0 Synopsis

<b>AbbVie Inc.</b>	<b>Individual Study Table Referring to Part of Dossier:</b> <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> ABT-493, ABT-530, ABT-493/ABT-530		
<b>Name of Active Ingredient:</b> <b>ABT-493:</b> (3 <i>aR</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> ,21 <i>E</i> ,24 <i>aR</i> )-7- <i>tert</i> -butyl- <i>N</i> -{(1 <i>R</i> ,2 <i>R</i> )-2-(difluoromethyl)-1-[(1-methylcyclopropane-1-sulfonyl)carbamoyl]cyclopropyl}-20,20-difluoro-5,8-dioxo-2,3,3 <i>a</i> ,5,6,7,8,11,12,20,23,24 <i>a</i> -dodecahydro-1 <i>H</i> ,10 <i>H</i> -9,12-methanocyclopenta[18,19][1,10,17,3,6]trioxadiazacyclononadecino[11,12- <i>b</i> ]quinoxaline-10-carboxamide hydrate <b>ABT-530:</b> methyl {(2 <i>S</i> ,3 <i>R</i> )-1-[(2 <i>S</i> )-2-{5-[(2 <i>R</i> ,5 <i>R</i> )-1-{3,5-difluoro-4-[4-(4-fluorophenyl) piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2 <i>S</i> )-1-[ <i>N</i> -(methoxycarbonyl)- <i>O</i> -methyl-Lthreonyl] pyrrolidin-2-yl}-1 <i>H</i> -benzimidazol-5-yl) pyrrolidin-2-yl]-6-fluoro-1 <i>H</i> benzimidazol-2-yl} pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl} carbamate		
<b>Title of Study:</b> A Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Co-Administration of ABT-493 and ABT-530 With and Without Ribavirin in Subjects With Chronic Hepatitis C Virus (HCV) Genotypes 2, 3, 4, 5, or 6 Infection (SURVEYOR-II)		
<b>Coordinating Investigator:</b> ██████████		
<b>Study Sites:</b> 81 sites in Australia, Canada, France, Korea, New Zealand, Taiwan, United Kingdom, and United States enrolled subjects		
<b>Publications:</b> 1 article, 5 abstracts		
<b>Studied Period (Years):</b> First Subject First Visit: 19 September 2014 Last Subject Last Visit for Primary Analysis: 25 October 2016	<b>Phase of Development:</b> 2	
<b>Objectives:</b> The primary objectives of Parts 1 to 4 of this study were to assess the efficacy and safety of ABT-493 and ABT-530 coadministered with or without ribavirin (RBV) in adults with chronic HCV genotype (GT) 2, 3, 4, 5, or 6 infection with or without cirrhosis. In addition, the primary objectives for Part 4 also included the assessment of the efficacy (sustained virologic response 12 weeks postdosing [SVR <sub>12</sub> ]) of treatment with the ABT-493/ABT-530 combination regimen in GT2-infected direct-acting antiviral agent (DAA)-naïve subjects without cirrhosis compared to a historical SVR <sub>12</sub> rate of treatment with sofosbuvir (SOF) plus RBV in GT2-infected DAA-naïve subjects without cirrhosis. The secondary objectives for the entire study were to assess the pharmacokinetics of ABT-493, ABT-530, and RBV and the emergence and persistence of viral variants with these treatment regimens.		

**Methodology:**

This was an expanded Phase 2, randomized, open-label, multipart, multicenter study. The study consisted of 4 independent parts, with Parts 1 and 2 representing the supportive/exploratory parts of the study and Parts 3 and 4 representing the confirmatory/registrational parts of the study.

In Part 1, GT2-infected treatment-naïve (TN) and treatment-experienced (TE) subjects without cirrhosis were randomized in a 1:1:1 ratio into 1 of 3 treatment arms:

Arm A: ABT-493 300 mg once daily (QD) + ABT-530 120 mg QD for 12 weeks

Arm B: ABT-493 200 mg QD + ABT-530 120 mg QD for 12 weeks

Arm C: ABT-493 200 mg QD + ABT-530 120 mg QD + RBV 1,000 mg or 1,200 mg (weight based) divided twice daily (BID) for 12 weeks

In Part 1, GT3-infected TN and TE subjects without cirrhosis were randomized in a 1:1:1:1 ratio into 1 of 4 treatment arms:

Arm D: ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks

Arm E: ABT-493 200 mg QD + ABT-530 120 mg QD for 12 weeks

Arm F: ABT-493 200 mg QD + ABT-530 120 mg QD + RBV 1,000 mg or 1,200 mg (weight based) divided BID for 12 weeks

Arm G: ABT-493 200 mg QD + ABT-530 40 mg QD for 12 weeks

Subjects were stratified in Part 1 by prior HCV treatment history (naïve or experienced).

Arms in Part 2 were enabled for enrollment based on prespecified safety and efficacy criteria for data from Part 1 Arms A – G, once all subjects in Part 1 had reached Post-Treatment Week 4. AbbVie determined which of the enabled arms in Part 2 would be enrolled. Based on favorable Part 1 results, all planned treatment arms in Part 2 were enabled per protocol. AbbVie decided to enroll enabled Arms J, L, O, and P in Part 2.

In Part 2, GT2-infected TN and TE subjects without cirrhosis were enrolled into:

Arm J: ABT-493 mg QD + ABT-590 120 mg QD for 8 weeks

In Part 2, GT3-infected TN and TE subjects without cirrhosis were enrolled into:

Arm L<sub>TN</sub>: ABT-493 300 mg QD + ABT-530 120 mg QD for 8 weeks

Arm L<sub>TE</sub>: ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks

In Part 2, GT3-infected TN subjects with cirrhosis were randomized in a 1:1 ratio into 1 of 2 treatment arms:

Arm O: ABT-493 300 mg QD + ABT-530 120 mg QD for 12 weeks

Arm P: ABT-493 300 mg QD + ABT-530 120 mg QD + RBV 800 mg QD for 12 weeks

Arms in Part 3 were enabled for enrollment of GT3-infected subjects based on prespecified criteria for efficacy data from Part 2 Arms L (TE cohort) and O (TN cohort) once all applicable subjects in Arms L and O had reached Post-Treatment Week 4. AbbVie determined which of the enabled arms in Part 3 for noncirrhotic and/or cirrhotic subjects would proceed to enrollment.

Noncirrhotic and/or cirrhotic subjects meeting all eligibility criteria were randomized in a 1:1 ratio into 1 of 2 treatment arms in Part 3 with randomization stratified by presence or absence of cirrhosis and by prior HCV treatment history (naïve or experienced) for cirrhotic subjects.

Arms Q and R in Part 3 for all GT3 cohorts (noncirrhotic and cirrhotic) were enabled based on the supporting data from Part 2 and the prespecified efficacy criteria.

**Methodology (Continued):**

In Part 3, GT3-infected TN subjects with cirrhosis were only enrolled into:

Arm Q: ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks

In Part 3, GT3-infected TE subjects without cirrhosis were randomized in a 1:1 ratio into 1 of 2 treatment arms:

Arm Q: ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks

Arm R: ABT-493/ABT-530 300 mg/120 mg QD for 16 weeks

In Part 3, GT3-infected TE subjects with cirrhosis were only enrolled into:

Arm R: ABT-493/ABT-530 300 mg/120 mg QD for 16 weeks

In Part 4, Approximately 100 GT2-infected and approximately 60 GT4 – 6-infected TN and TE subjects without cirrhosis were enrolled into:

Arm S: ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks

Safety and efficacy were assessed throughout the study.

In the Post-Treatment Period, all subjects administered at least 1 dose of study drug were followed for 24 weeks to monitor for safety, HCV RNA, and the emergence and/or persistence of resistance-associated variants. The planned duration of the study (excluding screening) was up to 40 weeks for all randomized subjects.

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

Planned: up to 685 subjects (approximately 175 subjects in Part 1; approximately 150 subjects in Part 2; approximately 200 subjects in Part 3, and approximately 160 subjects in Part 4).

Analyzed: 692 subjects (195 subjects in Part 1, 162 subjects in Part 2, 131 subjects in Part 3, and 203 subjects in Part 4) were randomized and received at least 1 dose of study drug.

**Diagnosis and Main Criteria for Inclusion:**

**Main Inclusion Criteria:**

- Male or female (of nonchildbearing potential, practicing total abstinence, sexually active with female partners only, or using approved contraceptive methods) between 18 and 70 years of age, inclusive (Parts 1 and 2) or at least 18 years old (Parts 3 and 4) at time of screening;
- Screening laboratory result indicating HCV GT2 (Parts 1, 2, or 4), HCV GT3 (Parts 1, 2, or 3), or GT4 – GT6 (Part 4) infection.
- Chronic HCV infection defined as 1 of the following:
  - Positive for anti-HCV antibody or HCV RNA at least 6 months before screening, and positive for HCV RNA and anti-HCV antibody at the time of screening, or
  - Positive for anti-HCV antibody and HCV RNA at the time of screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrollment with evidence of chronic HCV infection).
- Subject had to meet 1 of the following criteria:
  - TN (all arms): subject had never received treatment for HCV infection (not applicable to subjects without cirrhosis in Part 3)
  - TE (all arms in Parts 1, 3, and 4; Arm L in Part 2): previous pegIFN/RBV-experienced [Parts 1 and 2] or previous IFN or pegIFN ± RBV, or SOF plus RBV ± pegIFN-experienced (Parts 3 and 4)

**Diagnosis and Main Criteria for Inclusion (Continued):**

**Main Inclusion Criteria (Continued):**

- Documented as either noncirrhotic (Part 1: subjects in all arms; Parts 2, 3 and 4: subjects in Arms J and L [Part 2], Arms Q and R [Part 3, as applicable], and Arm S [Part 4]), or cirrhotic (GT3-infected subjects in Part 2 Arms O and P and Part 3 Arms Q and R [as applicable], per local standard).

**Main Exclusion Criteria:**

- History of severe, life-threatening or other clinically significant sensitivity to any study drug.
- Female who was pregnant, planning to become pregnant during the study, or breastfeeding; or male whose partner was pregnant or planning to become pregnant during the study.
- Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol, in the opinion of the investigator.
- Positive test result at screening for hepatitis B surface antigen or anti-human immunodeficiency virus antibody.
- HCV genotyping performed during screening indicated coinfection with more than 1 HCV genotype.
- Any cause of liver disease other than chronic HCV infection.
- Subjects with plasma HCV RNA load  $\leq 10,000$  IU/mL (Part 1 or 2) or  $\leq 1,000$  IU/mL (Part 3 or 4) or unquantifiable or undetectable HCV RNA (all parts) at screening.
- Previous use of any HCV DAA, except SOF (Parts 3 and 4 only).
- Consideration by the investigator, for any reason, that the subject was an unsuitable candidate to receive ABT-493, ABT-530, or RBV (Parts 1 and 2) or coformulated ABT-493/ABT-530 (Parts 3 and 4).
- For subjects in Parts 2 and 3 who were enrolling with cirrhosis: past clinical evidence of Child-Pugh B or C Classification (score of  $> 6$ ) or clinical history of liver decompensation, including ascites (noted on physical examination), bleeding varices, use of beta-blockers or diuretics for portal hypertension or ascites, or hepatic encephalopathy.

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

Investigational Product	Manufacturer	Dosage Form/Mode of Administration	Bulk Lot Number
ABT-493 (Parts 1 and 2 only)	AbbVie	100 mg tablet/oral	14-001033, 14-001291, 14-001290
ABT-530 (Parts 1 and 2 only)	AbbVie	40 mg tablet/oral	14-001596, 14-002134, 14-002133
ABT-493/ABT-530 (Parts 3 and 4 only)	AbbVie	100 mg tablet/ 40 mg tablet/oral	15-006020, 15-006595
RBV (Part 1) (Parts 1 and 2 only)	Roche or Generic Manufacturer	200 mg tablet/oral	13-005533, 14-001228 13-006235

**Duration of Treatment:**

Subjects received ABT-493 and ABT-530 (or ABT-493/ABT-530) with or without RBV for 8, 12, or 16 weeks.

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

Not applicable.

**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 of treatment.

**Resistance:**

For all subjects receiving study drug, the variants at signature resistance-associated amino acid positions at baseline identified by population or deep sequencing and comparison to the appropriate prototypic reference sequence were analyzed.

The following resistance information was analyzed for subjects receiving study drugs who did not achieve SVR<sub>12</sub> and who had a postbaseline sample with HCV RNA  $\geq$  1,000 IU/mL: 1) the amino acid variants in available postbaseline samples identified by population or deep nucleotide sequencing and comparison to the baseline sequence, 2) the amino acid variants in available postbaseline samples at signature resistance-associated positions identified by population or deep sequencing and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral resistance by population or deep nucleotide sequencing.

**Patient Reported Outcomes (PROs):**

Health state utility was measured using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L) instrument. Treatment satisfaction was assessed using the chronic HCV Treatment Satisfaction Instrument (HCVTSat). The Work Productivity and Activity Impairment Questionnaire: Hepatitis C (WPAI: Hepatitis C) assessed work and activity impairment due to HCV. The Fatigue Severity Scale (FSS) was used to measure the severity of fatigue and its effect on lifestyle and activities. The Short Form 36 Version 2 Health Status Survey (SF-36v2) was used to assess the functional health and well-being of subjects.

**Pharmacokinetics:**

Plasma concentrations and pharmacokinetic parameter values for ABT-493, ABT-530, and RBV were tabulated for each subject and study arm. Summary statistics were computed for each time and visit for intensive pharmacokinetic days.

**Safety:**

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

**Statistical Methods**

**Efficacy:**

The primary efficacy endpoint was the percentage of subjects who achieved SVR<sub>12</sub> (HCV RNA < lower limit of quantitation [LLOQ] 12 weeks after the last actual dose of study drug). For each arm, or for each population within an arm (e.g., TE subjects without cirrhosis in Arms Q and R), as applicable, the number and percentage of subjects achieving SVR<sub>12</sub> were summarized along with 95% confidence intervals using Wilson score intervals.

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

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

In Part 4, the percentage of GT2-infected DAA-naïve subjects without cirrhosis treated with ABT-493/ABT-530 who achieved SVR<sub>12</sub> would be noninferior to the historical 95% SVR<sub>12</sub> rate of the current standard of care (SOF + RBV for 12 weeks) in GT2-infected DAA-naïve subjects without cirrhosis if the lower confidence bound (LCB) of the 2-sided 95% confidence interval using normal approximation of the percentage of these subjects with SVR<sub>12</sub> was > 89%.

The secondary efficacy endpoints were:

- The percentage of subjects who achieved sustained virologic response 4 weeks postdosing (SVR<sub>4</sub>);
- The percentage of subjects with on-treatment virologic failure (defined as confirmed HCV RNA  $\geq$  LLOQ after HCV RNA < LLOQ during treatment, confirmed increase of > 1 log<sub>10</sub> IU/mL above nadir during treatment, or HCV RNA  $\geq$  LLOQ at end of treatment with at least 6 weeks of treatment);
- The percentage of subjects with post-treatment relapse (defined as confirmed HCV RNA  $\geq$  LLOQ between the end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment with HCV RNA < LLOQ at the end of treatment excluding reinfection [Relapse<sub>12</sub>]).

For each treatment arm, the number and percentage of subjects meeting each secondary efficacy endpoint were summarized along with 95% Wilson score intervals.

#### **Resistance:**

The following resistance information was analyzed for all baseline samples from subjects: 1) the prevalence of variants at signature amino acid positions or a key subset of amino acid at baseline identified by population sequencing or NGS were compared to the appropriate subtype specific prototypic reference sequence; and, (2) a comparison of SVR<sub>12</sub> rates in subjects with or without baseline variants was conducted. For subjects experiencing virologic failure, variants at postbaseline time points identified by population nucleotide sequencing or NGS were compared to the respective baseline sequence and to a subtype-specific reference sequence.

#### **HCV Genotype/Subtype:**

Phylogenetic analysis was conducted on all available HCV sequences from baseline samples in order to accurately determine HCV subtype.

#### **Subgroup:**

The percentage of subjects with SVR<sub>12</sub> was presented for subgroup variables, such as HCV GT2, GT3, GT4, GT5, and GT6 subtype, interleukin 28B genotype, prior HCV treatment history, and baseline HCV RNA level.

#### **Pharmacokinetics:**

Plasma concentrations of ABT-493, ABT-530, and RBV were tabulated for each subject and study arm. Summary statistics were computed for each time and visit for intensive pharmacokinetic days.

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

#### **Safety:**

All subjects who received at least 1 dose of study drugs were included in the safety analyses. Safety summaries were provided by treatment arm. The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that began or worsened in severity after initiation of study drug through 30 days after the last dose of study drug) were tabulated by Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>) primary system organ class and preferred term. The tabulation of the number of subjects with treatment-emergent AEs by severity grade (Grades 1 – 5) and relationship to study drug was also provided. Mean changes from baseline in laboratory tests and vital signs to each postbaseline visit were summarized. The number and percentage of subjects with postbaseline values meeting toxicity grades and meeting potential hepatotoxicity criteria were summarized. The number and percentage of subjects with postbaseline values meeting predefined criteria for potentially clinically significant vital sign values during treatment were summarized by treatment group.

### **Summary/Conclusions**

#### **Efficacy and Resistance Results:**

#### **Parts 1 and 2**

#### ***Efficacy***

- HCV GT2-infected subjects without cirrhosis treated with ABT-493 and ABT-530 QD for 8 weeks or 12 weeks achieved high efficacy (SVR<sub>12</sub> rates of 96% – 100%), across all doses studied, with no virologic failures observed.
- The dose regimen of ABT-493 300 mg and ABT-530 120 mg QD achieved high SVR<sub>12</sub> rates and maximized efficacy in HCV GT3-infected subjects with or without cirrhosis.
  - TN GT3-infected subjects with or without cirrhosis receiving ABT-493 300 mg + ABT-530 120 mg QD for a duration of 12 weeks achieved high efficacy (SVR<sub>12</sub> rate of 98%) and shortening the treatment duration to 8 weeks for subjects without cirrhosis resulted in similarly high efficacy (SVR<sub>12</sub> rate of 97%), with no virologic failures observed.
  - A higher relapse rate with the regimen of ABT-493 300 mg + ABT-530 120 mg QD for 12 weeks was observed in noncirrhotic GT3-infected subjects with treatment experience compared to those naïve to treatment (8% versus 0%), indicating that extending treatment duration may improve efficacy in TE subjects.
- Efficacy of ABT-493 and ABT-530 was similarly high regardless of RBV coadministration for both HCV GT2- and GT3-infected subjects, indicating that RBV may not be needed to increase SVR rates for this regimen.
- Among HCV GT2-infected and TN GT3-infected subjects treated with ABT-493 300 mg + ABT-530 120 mg QD, high efficacy was observed regardless of baseline host or viral factors, including subgenotype, baseline HCV RNA levels, fibrosis stage, or presence of baseline NS3 and/or NS5A polymorphisms.
- No subjects relapsed after achieving SVR<sub>12</sub>.



**Summary/Conclusions (Continued)**

**Efficacy and Resistance Results (Continued):**

**Parts 1 and 2 (Continued)**

***Resistance***

The prevalence of baseline polymorphisms at key amino acid positions was 0.8% (1/125) in NS3 and 72.0% (90/125) in NS5A in GT2-infected subjects across all arms in Parts 1 and 2 of the study. None of the GT2-infected subjects experienced virologic failure, indicating that baseline polymorphisms had no impact on treatment outcome in GT2-infected subjects.

The prevalence of baseline polymorphisms at key amino acid positions was 3.1% (7/229) in NS3 and 22.3% (51/229) in NS5A in GT3-infected subjects across all arms in Parts 1 and 2 of the study. Eight of the 10 (80%) GT3a-infected subjects who experienced virologic failure in Parts 1 and 2 had baseline polymorphisms at signature amino acid positions in NS3 and/or NS5A. However, due to the low prevalence of polymorphisms coupled with the low number of virologic failures within each arm, trends in impact of baseline polymorphisms on treatment outcome in GT3a-infected subjects could not be assessed.

**Part 3**

***Efficacy***

Treatment-naïve subjects with cirrhosis achieved a SVR<sub>12</sub> rate of 98% (39/40) and TE subjects with cirrhosis achieved a SVR<sub>12</sub> rate of 96% (45/47) following 12 and 16 weeks of treatment, respectively, with no virologic failures among TN subjects with cirrhosis. Among TE subjects without cirrhosis, the SVR<sub>12</sub> rates for the 12-week (Arm Q) and 16-week (Arm R) regimens were 91% (20/22) and 95% (21/22), respectively; the difference was not statistically significant.



**Summary/Conclusions (Continued)**

**Efficacy and Resistance Results (Continued):**

**Part 3 (Continued)**

**Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR<sub>12</sub>) – Part 3 (ITT Population GT3-Infected Subjects)**

Assessment	Number (%) of GT3-Infected Subjects Treated with ABT-493/ABT-530 300 mg/120 mg QD			
	No Cirrhosis		Cirrhosis	
	TE	TN	TE	TN
	Arm Q × 12 Weeks N = 22	Arm R × 16 Weeks N = 22	Arm Q × 12 Weeks N = 40	Arm R × 16 Weeks N = 47
SVR <sub>12</sub> , n/N (%)	20/22 (90.9)	21/22 (95.5)	39/40 (97.5)	45/47 (95.7)
95% CI	(72.2, 97.5)	(78.2, 99.2)	(87.1, 99.6)	(85.8, 98.8)
Nonresponse, n/N (%)	2/22 (9.1)	1/22 (4.5)	1/40 (2.5)	2/47 (4.3)
Reason for nonresponse, n/N (%)				
Virologic failure	2/22 (9.1)	1/22 (4.5)	0/40	2/47 (4.3)
On-treatment virologic failure	0/22	0/22	0/40	1/47 (2.1)
Relapse	2/22 (9.1)	1/22 (4.5)	0/39	1/46 (2.2)
Nonvirologic failure	0/22	0/22	1/40 (2.5)	0/47
Premature study drug discontinuation	0/22	0/22	0/40	0/47
HCV reinfection	0/22	0/22	0/40	0/47
Missing SVR <sub>12</sub> data	0/22	0/22	1/40 (2.5)	0/47
Other	0/22	0/22	0/40	0/47

CI = confidence interval; GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat; QD = once daily; RNA = ribonucleic acid; SVR = sustained virologic response; SVR<sub>12</sub> = sustained virologic response 12 weeks postdosing; TE = treatment-experienced; TN = treatment-naïve

Note: 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)**

**Efficacy and Resistance Results (Continued):**

**Part 3 (Continued)**

***Resistance***

Baseline polymorphisms at the key subset of amino acid positions in NS3 (positions 155, 156, or 168) were detected in 1.6% (2/129) of the GT3-infected subjects. NS5A polymorphisms (at positions 24, 28, 30, 31, 58, 92, or 93) were detected in 18.6% (24/129) of the GT3-infected subjects. None of the TE GT3-infected subjects without cirrhosis randomized to the 12-week Arm Q2 or 16-week Arm R1 had NS3 polymorphisms at any of the key subset of amino acid positions. The prevalence of NS5A polymorphisms at the key subset of amino acid positions was higher among TE GT3-infected subjects without cirrhosis randomized to the 12-week Arm Q2 (6/22, 27.3%) compared to the 16-week R1 (3/21, 14.3%).

The presence of baseline polymorphisms did not impact treatment outcome in TN and TE GT3-infected subjects with cirrhosis treated for 12 and 16 weeks, respectively.

Among TE GT3-infected subjects without cirrhosis randomized to the 12-week Arm Q2 and 16-week Arm R1, the SVR<sub>12</sub> rates were similarly lower (4/6, 66.7% in Arm Q2 and 2/3, 66.7% in Arm R1) in the presence of NS5A baseline polymorphisms at a key subset of amino acid positions. However, when considering all TE subjects (with or without cirrhosis) in Arm R, the SVR<sub>12</sub> rate in the presence of NS5A polymorphisms was higher with 16 weeks of treatment (8/9, 88.9%) compared to 12 weeks of treatment. Two TE subjects without cirrhosis that experienced virologic failure had the A30K baseline polymorphism. The prevalence of A30K among GT3-infected TE subjects without cirrhosis was low in both the 12-week Arm Q2 (4.5%, 1/22) and the 16-week Arm R1 (4.8%, 1/21). Given the low prevalence of A30K in GT3-infected subjects in Part 3 and across the different arms of this study (5.3%, 19/358) and the high SVR<sub>12</sub> rates achieved in TE GT3-infected subjects, it is unlikely that this polymorphism has a significant impact on treatment outcome in this population.

**Part 4**

***Efficacy***

Overall, the SVR<sub>12</sub> rate was 97% (196/203) and relapse rates were 1% (2/201) following 8 weeks of treatment for GT2- and GT4 – 6-infected subjects without cirrhosis. Noninferiority of 8 weeks of treatment for DAA-naïve GT2-infected subjects to the historical control (SOF + RBV for 12 weeks) was demonstrated, as the 95% LCB for SVR<sub>12</sub> was > 89%. Among GT4 – 6-infected subjects, individual genotype SVR<sub>12</sub> rates were all ≥ 90%, with no virologic failures observed.

**Summary/Conclusions (Continued)**

**Efficacy and Resistance Results (Continued):**

**Part 4 (Continued)**

**Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR<sub>12</sub>) – Part 4 (ITT Population GT2- and GT4 – 6-Infected Subjects)**

Assessment	Arm S ABT-493/ABT-530 300 mg/120 mg QD × 8 Weeks	
	GT2-Infected, No Cirrhosis, TN and TE N = 145 <sup>a</sup>	GT4 – 6-Infected, No Cirrhosis, TN and TE N = 58
SVR <sub>12</sub> , n/N (%)	142/145 (97.9)	54/58 (93.1)
95% CI	94.1, 99.3	83.6, 97.3
Nonresponse, n/N (%)	3/145 (2.1)	4/58 (6.9)
Reason for nonresponse, n/N (%)		
Virologic failure	2/145 (1.4)	0/58
On-treatment virologic failure	0/145	0/58
Relapse	2/144 (1.4)	0/57
Nonvirologic failure	1/145 (0.7)	4/58 (6.9)
Premature study drug discontinuation	1/145 (0.7)	1/58 (1.7)
HCV reinfection	0/145	0/58
Missing SVR <sub>12</sub> data	0/145	3/58 (5.2)
Other	0/145	0/58

CI = confidence interval; GT = genotype; HCV = hepatitis C virus; ITT = intention-to-treat; QD = once daily; RNA = ribonucleic acid; SVR = sustained virologic response; SVR<sub>12</sub> = sustained virologic response 12 weeks postdosing; TE = treatment-experienced; TN = treatment-naïve

a. This number includes 2 subjects who enrolled as HCV GT2 who were later determined to be GT1 based on phylogenetic analysis of baseline sequence.

Note: 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)**

**Efficacy and Resistance Results (Continued):**

**Part 4 (Continued)**

***Resistance***

Baseline polymorphisms at the key subset of amino acid positions in NS3 (positions 155, 156, or 168) were detected in 0.8% (1/125), 2.4% (1/41), and 0% (0/6) of the GT2-, GT4-, and GT6-infected subjects, respectively. The NS5A polymorphisms (at positions 24, 28, 30, 31, 58, 92, or 93) were detected in 76.2% (96/126), 43.9% (18/41), and 57.1% (4/7) of the GT2-, GT4-, and GT6-infected subjects, respectively. The single GT5-infected subject with resistance data available did not have baseline polymorphisms in NS3 or NS5A.

The presence of baseline polymorphisms had no impact on treatment outcome in subjects infected with any HCV genotype/subtype in Part 4 of this study.

**Safety Results:**

**Parts 1 and 2:**

The ABT-493 and ABT-530 regimens with or without RBV were well tolerated. The frequency of AEs was comparable across doses tested; no dose-dependency was observed for any AE. The majority of subjects with AEs experienced events with a maximum severity of Grade 1 (mild), with the 3 most common AEs overall being headache, fatigue, and nausea. The most common AEs were more prevalent in regimens containing RBV. Adverse events leading to study drug discontinuation and study drug-related serious adverse events (SAEs) were rare (< 1% of subjects) and there were no AEs leading to death. Clinically significant laboratory abnormalities were infrequent and did not lead to premature treatment discontinuation. No cases of drug-induced liver injury or hepatic decompensation were identified. There was a comparable safety profile regardless of duration of treatment with study drug (8 or 12 weeks) and between subjects with and without cirrhosis, including subjects with cirrhosis who were exposed to the highest dose regimen of ABT-493 300 mg and ABT-530 120 mg without RBV. No safety signals were identified.

**Part 3:**

The fixed dose combination of ABT-493/ABT-530 300 mg/120 mg QD was well tolerated. The majority of subjects with AEs experienced events with a maximum severity of Grade 1 (mild), with the 3 most common AEs overall being fatigue, headache, and nausea. No subject experienced a study drug-related SAE, an AE leading to premature study drug discontinuation, or an AE leading to death. Clinically significant laboratory abnormalities were infrequent and did not lead to premature treatment discontinuation. No cases of drug-induced liver injury or hepatic decompensation were identified. There was a comparable safety profile regardless of duration of treatment with study drug (12 or 16 weeks) and between subjects with or without cirrhosis. No safety signals were identified.

**Part 4:**

The fixed-dose combination of ABT-493/ABT-530 300 mg/120 mg QD in subjects without cirrhosis treated for 8 weeks was well tolerated. The majority of subjects with AEs experienced events with a maximum severity of Grade 1 (mild), with the 3 most common AEs overall being fatigue, headache, and nausea. No subject experienced a study drug-related SAE, an AE leading to premature study drug discontinuation, or an AE leading to death. Clinically significant laboratory abnormalities were infrequent and did not lead to premature treatment discontinuation. No cases of drug-induced liver injury or hepatic decompensation were identified. No safety signals were identified.

**Summary/Conclusions (Continued)**

**Conclusions:**

**Parts 1 and 2 (Exploratory/Supportive)**

- ABT-493 300 mg and ABT-530 120 mg QD doses maximized efficacy without the need for RBV coadministration. Eight weeks in HCV GT2-infected and TN GT3-infected subjects without cirrhosis resulted in high efficacy with no virologic failures. Slightly higher relapse rates were observed in TE GT3-infected subjects.
- At the optimal dose, high efficacy among HCV GT2-infected and TN GT3-infected subjects was observed regardless of baseline host or viral factors, including subgenotype, baseline HCV RNA levels, fibrosis stage, or presence of baseline NS3 and/or NS5A polymorphisms.
- ABT-493 and ABT-530 demonstrated a favorable safety profile and was well tolerated across all doses tested (including subjects with cirrhosis exposed to ABT-493 300 mg and ABT-530 120 mg QD), with mostly mild AEs, rare occurrences of clinically significant laboratory abnormalities, and low rates of both discontinuations due to AEs and study drug-related SAEs. The most common AEs were more prevalent in regimens containing RBV. Safety profiles were comparable between subjects with and without cirrhosis.

**Part 3 (Confirmatory/Registrational)**

- TN HCV GT3-infected subjects with cirrhosis treated with ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks achieved high efficacy (SVR<sub>12</sub> rate of 98%), with no virologic failures.
- TE HCV GT3-infected subjects with or without cirrhosis treated with ABT-493/ABT-530 300 mg/120 mg QD for 16 weeks achieved high efficacy (SVR<sub>12</sub> rates > 95%) with low relapse rates of 2 – 5%, while the shorter treatment duration of 12 weeks among subjects without cirrhosis resulted in a slightly lower SVR<sub>12</sub> rate (91%) and a slightly higher relapse rate (9%).
- Among TN HCV GT3-infected subjects with cirrhosis treated for 12 weeks and TE HCV GT3-infected subjects with or without cirrhosis treated for 16 weeks, similarly high efficacy was observed regardless of baseline host or viral factors, including baseline HCV RNA levels, type of prior treatment experience (IFN- or SOF-based), subgenotype, fibrosis stage, or presence of baseline NS3 and/or NS5A polymorphisms.
- ABT-493/ABT-530 300 mg/120 mg QD demonstrated a favorable safety profile and was well tolerated, with mostly mild AEs, rare occurrences of clinically significant laboratory abnormalities, and no study drug-related SAEs or discontinuations due to AEs. Safety profiles were comparable regardless of treatment duration (12 and 16 weeks) and between subjects with and without cirrhosis.

**Summary/Conclusions (Continued)**

**Conclusions (Continued):**

**Part 4 (Confirmatory/Registrational)**

- TN and TE HCV GT2- and GT4 – 6-infected subjects without cirrhosis treated with ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks achieved high efficacy (SVR<sub>12</sub> rate of 97%), with a similarly low relapse rate (1%) compared with 12-week regimens. Treatment of DAA-naïve HCV GT2-infected subjects for 8 weeks was noninferior to the current standard-of-care (SOF/RBV for 12 weeks). There were no virologic failures among GT4 – 6-infected subjects.
- High efficacy was observed regardless of baseline host or viral factors, including baseline HCV RNA levels, prior treatment experience, type of prior treatment experience (IFN- or SOF-based), subgenotype, fibrosis stage, or presence of baseline NS3 and/or NS5A polymorphisms.
- ABT-493/ABT-530 300 mg/120 mg QD demonstrated a favorable safety profile and was well tolerated, with mostly mild AEs, rare occurrences of clinically significant laboratory abnormalities, and no study drug-related SAEs or discontinuations due to AEs.

**Pharmacokinetics (Parts 1 – 4)**

- Pharmacokinetic exposures of ABT-493 were comparable following administration of the ABT-493 100 mg tablet and ABT-493 100 mg/ABT-530 40 mg film-coated tablet formulation at the equivalent dose. Pharmacokinetic exposures of ABT-493 following administration of 300 mg were approximately 1- to 2-fold higher than exposures following administration of 200 mg. Pharmacokinetic exposures of ABT-493 in Arms B, C, E, and F (dose level of ABT-493 200 mg and ABT-530 120 mg QD) were similar to the ABT-493 exposure in Arm G (dose level of ABT-493 200 mg and ABT-530 40 mg QD). Following administration of ABT-493 100 mg tablet and ABT-493 100 mg/ABT-530 40 mg film-coated tablet formulations at the equivalent dose, pharmacokinetic exposures of ABT-493 in subjects with cirrhosis were approximately 1- to 2-fold higher than subjects without cirrhosis.
- Pharmacokinetic exposures of ABT-530 were comparable following administration of the ABT-530 40 mg tablet and ABT-493 100 mg/ABT-530 40 mg film-coated tablet formulation at the equivalent dose. Pharmacokinetic exposures of ABT-530 following administration of 120 mg were approximately 2- to 3-fold higher than exposures following administration of 40 mg. Following administration of the ABT-530 40 mg tablet and ABT-493 100 mg/ABT-530 40 mg film-coated tablet formulation at the dose level of ABT-493 300 mg and ABT-530 120 mg QD, pharmacokinetic exposures of ABT-530 in subjects without cirrhosis were similar to the ABT-530 exposures in subjects with cirrhosis.