

## 2.0 Synopsis

AbbVie Inc.	<b>Individual Study Table Referring to Part of Dossier:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> ABT-493, ABT-530, ABT-493/ABT-530	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> <b>ABT-493:</b> (3aR,7S,10S,12R,21E,24aR)-7-tert-butyl-N-((1R,2R)-2-(difluoromethyl)-1-[(1-methylcyclopropane-1-sulfonyl)carbamoyl]cyclopropyl)-20,20-difluoro-5,8-dioxo-2,3,3a,5,6,7,8,11,12,20,23,24a-dodecahydro-1H,10H-9,12-methanocyclopenta[18,19][1,10,17,3,6]trioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide hydrate <b>ABT-530:</b> methyl {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorophenyl) piperidin-1-yl]phenyl} - 5-(6-fluoro-2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-Lthreonyl]pyrrolidin-2-yl} -1H-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl} carbamate.	<b>Page:</b>	
<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 (or ABT-493/ABT-530) With and Without Ribavirin in Adults With Chronic Hepatitis C Virus (HCV) Infection Who Failed a Prior Direct-Acting Antiviral Agent (DAA)-Containing Therapy		
<b>Coordinating Investigator:</b> ████████████████████		
<b>Study Sites:</b> 31 sites in Australia, France, Spain, the United Kingdom, and the United States (and its territory, Puerto Rico)		
<b>Publications:</b> 1 abstract		
<b>Studied Period (Years):</b> First Subject First Visit: 23 April 2015 Last Subject Last Visit for Primary Analysis: 13 October 2016	<b>Phase of Development:</b> 2	

**Objectives:**

The primary objectives in Part 1 of this study were to assess the efficacy and safety of ABT-493 and ABT-530 with or without ribavirin (RBV) in adults with chronic HCV genotype (GT) 1 infection who previously failed treatment with a DAA-containing regimen. The arm(s) in Part 2 of the study, which met the prespecified efficacy and safety criteria, were studied in Part 2 of the study, where the efficacy and safety of the regimen were confirmed by evaluating it in a broader and larger subject population.

The secondary objectives in Part 1 of the study were to assess the pharmacokinetics of ABT-493, ABT-530, and RBV, and to evaluate the role of RBV.

**Methodology:**

This was an expanded Phase 2, randomized, open-label, multicenter study, consisting of 2 parts (Part 1 and Part 2), to evaluate efficacy, safety, and pharmacokinetics of coadministration of ABT-493 and ABT-530 with or without RBV in subjects with chronic GT1 (Parts 1 and 2) or GT4 – GT6 (Part 2) HCV infection who failed a prior anti-HCV DAA-containing regimen.

For Part 1, approximately 50 subjects were to be enrolled and randomized in a 1:1:1 ratio to one of 3 treatment arms:

Arm A: ABT-493 200 mg once daily (QD) + ABT-530 80 mg QD for 12 weeks

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

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

Enrollment in Arm A was stopped with Amendment 3 based upon the decision not to pursue development of the doses in Arm A (ABT-493 200 mg QD + ABT-530 80 mg QD). Subjects were subsequently randomized in a 1:1 ratio to Arms B or C, with 20 subjects each in Arms B and C. Randomization in Part 1 was stratified by HCV GT1 subtype (1b or non-1b) and by previous experience to any of the 3 following DAA regimen classes:

1. Any experience with a nonstructural viral protein 5A (NS5A) inhibitor ( $\pm$  protease inhibitors [PI]) (e.g., daclatasvir [DCV] + sofosbuvir [SOF], DCV + asunaprevir, DCV + simeprevir [SMV], ledipasvir + SOF, ombitasvir + paritaprevir/ritonavir); or
2. NS5A inhibitor-naïve/PI-experienced (e.g., SMV + SOF, SMV + pegylated interferon and RBV [PR], telaprevir + PR, boceprevir + PR); or
3. All other previous DAA-containing regimens not captured above (e.g., SOF + PR, SOF + RBV).

Part 2 of the study was initiated based on meeting efficacy and safety criteria in Part 1. Approximately 80 HCV GT1- or GT4 – GT6-infected, DAA treatment-experienced subjects with compensated liver disease with or without cirrhosis were to be randomized in a 1:1 ratio to one of 2 treatment arms:

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

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

Randomization in Part 2 was stratified by HCV genotype (GT1 or GT4 – GT6) and by previous experience to the following 2 DAA regimen classes:

1. NS5A inhibitor ( $\pm$  PI)-experienced, limited to DCV-, ledipasvir-, or ombitasvir-containing combination regimens; or
2. NS5A inhibitor-naïve/nonstructural viral protein 3/4A (NS3/4A) PI-experienced, limited to: paritaprevir/ritonavir-, SMV-, telaprevir-, or boceprevir-containing combination regimens.

Safety and efficacy were assessed throughout the study. As this was an open-label study, the safety data were reviewed by AbbVie during the Treatment Period of the study.

**Methodology (Continued):**

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 polymorphisms. The planned total duration of the study (excluding screening) was up to 40 weeks for all randomized subjects.

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

Planned: up to 130 subjects (approximately 50 subjects in Part 1; approximately 80 subjects in Part 2).  
Analyzed: 141 subjects (50 in Part 1 and 91 in Part 2) 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 allowed contraceptive methods) between 18 and 70 years of age (inclusive) in Part 1 or at least 18 years old in Part 2 at time of screening.
- Screening laboratory result indicating HCV GT1 infection in Part 1 or HCV GT1 or GT4 – GT6 in Part 2.
- 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), or
  - Positive for anti-HCV antibody and HCV RNA at the time of screening with abnormal alanine aminotransferase (ALT) levels for at least 6 months before screening.
- Subject had to meet one of the following criteria:
  - A history of previous DAA-containing treatment
  - On-treatment failure of the prior DAA-containing treatment regimen
  - Post-treatment relapseTreatment must have been completed at least 1 month prior to the Screening Visit.
- Subject must have been documented as noncirrhotic (Parts 1 and 2) or cirrhotic (Part 2 only) per local standard.
- For subjects in Part 2 who were enrolling with cirrhosis: must have had compensated cirrhosis defined as Child-Pugh score of  $\leq 6$  at screening and no current or past clinical evidence of Child-Pugh B or C classification or clinical history, including on Day 1 prior to dose 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.

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

**Main Inclusion Criteria (Continued):**

- For subjects in Part 2 who were enrolling with cirrhosis: absence of hepatocellular carcinoma as indicated by serum alpha fetoprotein < 100 ng/mL at screening and either a negative for hepatocellular carcinoma ultrasound, computed tomography scan, or magnetic resonance imaging scan within 3 months prior to screening, or a negative ultrasound at screening. Subjects who had an ultrasound with results suspicious of hepatocellular carcinoma followed by a subsequent negative computed tomography or magnetic resonance imaging scan of the liver were eligible for the study.

**Main Exclusion Criteria:**

- History of severe, life-threatening or other clinically significant sensitivity to any study drug or drug component.
- 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.
- Hepatitis C virus 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 (< 1,000 in Part 2) or unquantifiable or undetectable HCV RNA at screening.
- Previous exposure to ABT-493 or ABT-530.
- Consideration by the investigator, for any reason, that the subject was an unsuitable candidate to receive ABT-493, ABT-530, or RBV.

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

Investigational Product	Manufacturer	Dosage Form/Mode of Administration	Bulk Lot Number
ABT-493 (Part 1)	AbbVie	100 mg tablet/oral	14-001290
ABT-530 (Part 1)	AbbVie	40 mg tablet/oral	14-002133
Ribavirin (Part 1)	Roche or Generic Manufacturer	200 mg tablet/oral	14-001228
ABT-493/ABT-530 film-coated tablet (Part 2)	AbbVie	100 mg/40 mg tablet/oral	16-001003 15-006595

**Duration of Treatment:**

Subjects in Part 1 received ABT-493 and ABT-530 for 12 weeks.  
Subjects in Part 2 received ABT-493/ABT-530 for 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 in available samples at signature amino acid positions in NS3 and NS5A at baseline identified by next-generation sequencing (NGS) 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 sustained virologic response 12 weeks post dosing (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 NGS and comparison to the baseline sequences, 2) the amino acid variants in available postbaseline samples at signature positions identified by NGS and comparison to the appropriate prototypic reference sequences, and 3) the persistence of viral resistance by NGS.

**Pharmacokinetics:**

Plasma concentrations and pharmacokinetic parameter values for ABT-493, ABT-530, and RBV were tabulated for each subject and group.

**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 treatment arm, the number and percentage of subjects achieving SVR<sub>12</sub> were summarized along with a 95% confidence interval (CI) using Wilson score interval.

In addition, the difference in SVR<sub>12</sub> rates between treatment arms was analyzed using the stratum-adjusted Mantel-Haenszel proportion with a continuity correction for variance, adjusting for each of the randomization stratum.

The secondary endpoints were:

- The percentage of subjects who achieved sustained virologic response 4 weeks postdosing (HCV RNA < LLOQ 4 weeks after the last actual dose of study drug);
- The percentage of subjects with on-treatment virologic failure (defined as confirmed HCV RNA  $\geq$  100 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).

**Statistical Methods (Continued)**

**Efficacy (Continued):**

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 polymorphisms at signature amino acid positions or a key subset of amino acid positions 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 polymorphisms was conducted.

**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 genotype subtype (1a, 1b, 4a, etc.), interleukin 28B genotype, baseline HCV RNA level, and previous DAA regimen class.

**Pharmacokinetics:**

Plasma concentrations of ABT-530, ABT-493, and RBV and pharmacokinetic parameter values for ABT-493 and ABT-530 were tabulated for each subject and group. Summary statistics were computed for each time and visit.

**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 AEs (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<sup>®</sup> primary system organ class and preferred term. The tabulation of the number of subjects with 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 descriptively. 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:**

**Part 1**

*Efficacy:*

Overall SVR<sub>12</sub> rates were > 86% in all treatment arms in Part 1; only 2 subjects (1 each in Arms B and C, both of whom were NS5A + PI experienced) experienced virologic failure. The virologic failure rate among those with available SVR<sub>12</sub> data in Arms B and C was the same at 4.5% (1/22), suggesting that the presence of RBV in the regimen does not improve efficacy.

**Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR<sub>12</sub>) – Part 1 (ITT Population)**

Assessment	Arm A	Arm B	Arm C
	200 mg + 80 mg <sup>a</sup> QD × 12 Weeks N = 6	300 mg + 120 mg <sup>a</sup> + RBV 800 mg QD × 12 Weeks N = 22	300 mg + 120 mg <sup>a</sup> QD × 12 Weeks N = 22
SVR <sub>12</sub> , n/N (%)	6/6 (100)	21/22 (95.5)	19/22 (86.4)
95% CI <sup>b</sup>	61.0, 100.0	78.2, 99.2	66.7, 95.3
Nonresponse, n/N (%)	0/6	1/22 (4.5)	3/22 (13.6)
Reason for nonresponse, n/N (%)			
Virologic failure	0/6	1/22 (4.5)	1/22 (4.5)
On-treatment virologic failure	0/6	0/22	1/22 (4.5)
Relapse	0/6	1/21 (4.8)	0/21
Non-virologic failure	0/6	0/22	2/22 (9.1)
Premature study drug discontinuation	0/6	0/22	0/22
HCV reinfection	0/6	0/22	0/22
Missing SVR <sub>12</sub> data <sup>c</sup>	0/6	0/22	2/22 (9.1)
Other	0/6	0/22	0/22

CI = confidence interval; HCV = hepatitis C virus; ITT = intent-to-treat; LLOQ = lower limit of quantification; QD = once daily; RBV = ribavirin; RNA = ribonucleic acid; SVR = sustained virologic response; SVR<sub>12</sub> = sustained virologic response 12 weeks postdosing

- Dose of ABT-493 and ABT-530, respectively.
- Confidence interval constructed using the Wilson score method.
- These 2 subjects had demonstrated HCV RNA < LLOQ at Post-Treatment Week 8 but were considered nonresponders because no HCV RNA values in the SVR<sub>12</sub> window were available.

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 imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.

**Summary/Conclusions (Continued)**

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

**Part 1 (Continued)**

SVR<sub>12</sub> was achieved by the majority of study subjects, with a high efficacy rate across treatment arms and regardless of demographic or baseline characteristics, such as baseline HCV RNA, interleukin 28B, race, body mass index, gender, and age, including presence of baseline polymorphisms and time since last DAA treatment.

*Resistance:*

The prevalence of baseline polymorphisms at the key subset of amino acid positions 155, 156, or 168 in NS3, or 24, 28, 30, 31, 58, 92, or 93 in NS5A at 15% NGS detection threshold was 7.1% (3/42) in NS3 and 42.9% (18/42) in NS5A in GT1a-infected subjects, and 25.0% (2/8) in NS3 and 75.0% (6/8) in NS5A in GT1b-infected subjects across all arms in Part 1 of the study. Baseline polymorphisms across both NS3 and NS5A at the key amino acid positions at 15% NGS detection threshold were detected in 4.8% (2/42) of the GT1a-infected subjects, 25.0% (2/8) of the GT1b-infected subjects, and 8% (4/50) of GT1-infected subjects overall. The majority of subjects with a detected baseline polymorphism in NS3 or NS5A achieved SVR<sub>12</sub>. Two GT1a-infected NS5A-experienced/PI-experienced subjects, 1 each in Arms B and C, experienced virologic failure. The subject in Arm B with relapse had no baseline polymorphisms in NS3 and had L31M and H58D in NS5A. The subject in Arm C with breakthrough had Y56H and D168A/T in NS3 and had M28V, Q30R, and H58C in NS5A at baseline. Due to the limited number of failures, no clear impact of NS3 and/or NS5A baseline polymorphisms on treatment outcome was observed in Part 1 of the study.

**Part 2**

*Efficacy:*

Overall SVR<sub>12</sub> rates were > 88% in both treatment arms in Part 2. Twelve weeks of treatment with ABT-493/ABT-530 300 mg/120 mg QD was as effective as 16 weeks. Although the SVR<sub>12</sub> rates were similar, the relapse rate was lower in the 16 week treatment Arm E (0/43, 0%) compared with the 12 week treatment Arm D (4/43, 9.3%).

<b>Summary/Conclusions (Continued)</b>			
<b>Efficacy and Resistance Results (Continued):</b>			
<b>Part 2 (Continued)</b>			
<b>Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR<sub>12</sub>) – Part 2 (ITT Population)</b>			
<b>Assessment</b>	<b>Arm D ABT-493/ABT-530 300 mg/120 mg QD × 12 Weeks N = 44</b>	<b>Arm E ABT-493/ABT-530 300 mg/120 mg QD × 16 Weeks N = 47</b>	<b>Arms D + E N = 91</b>
SVR <sub>12</sub> , n/N (%)	39/44 (88.6)	43/47 (91.5)	82/91 (90.1)
95% CI <sup>a</sup>	76.0, 95.0	80.1, 96.6	82.3, 94.7
Nonresponse, n/N (%)	5/44 (11.4)	4/47 (8.5)	9/91 (9.9)
Reason for nonresponse, n/N (%)			
Virologic failure	5/44 (11.4)	4/47 (8.5)	9/91 (9.9)
On-treatment virologic failure	1/44 (2.3)	4/47 (8.5)	5/91 (5.5)
Relapse	4/43 (9.3)	0/43	4/86 (4.7)
Non-virologic failure	0/44	0/47	0/91
Premature study drug discontinuation	0/44	0/47	0/91
HCV reinfection	0/44	0/47	0/91
Missing SVR <sub>12</sub> data	0/44	0/47	0/91
Other	0/44	0/47	0/91
CI = confidence interval; HCV = hepatitis C virus; ITT = intent-to-treat; QD = once daily; RNA = ribonucleic acid; SVR = sustained virologic response; SVR <sub>12</sub> = sustained virologic response 12 weeks postdosing			
a. Confidence interval constructed using the Wilson score method.			
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 imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.			
SVR <sub>12</sub> was achieved by the majority of subjects in Part 2, with a high efficacy rate in each treatment arm and regardless of demographic or baseline characteristics, such as age, gender, race, body mass index, former injection drug user, HCV genotype, HCV RNA, IL28B, and fibrosis stage. The Relapse <sub>12</sub> rate was lower in Arm E compared with Arm D. Key subgroup analyses results are the following:			

**Summary/Conclusions (Continued)**

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

**Part 2 (Continued)**

- PI-experienced/NS5A-naïve subjects had an SVR<sub>12</sub> rate of 100% (14/14 in Arm D and 13/13 in Arm E).
- SVR<sub>12</sub> rates in subjects who were both NS5A- and PI-experienced were 78.6% (11/14) for 12 weeks of treatment and 81.3% (13/16) for 16 weeks of treatment.
- NS5A-experienced/PI-naïve subjects had a higher SVR<sub>12</sub> rate with 16 weeks (94.4% [17/18]) versus 12 weeks (87.5% [14/16]) of treatment, with more relapses in the 12-week arm (0 versus 1)

Across both arms, subjects who were both NS5A- and PI-experienced had a higher rate of virologic failure (20.0% [6/30]) compared with NS5A-experienced/PI-naïve (8.8% [3/34]) and PI-experienced/NS5-naïve (0% [0/27]) subjects.

*Resistance:*

Of the 91 subjects in the ITT population, 89 had HCV NS3/4A or NS5A baseline sequences available for phylogenetic analysis, and the number of subjects infected with each of the following HCV subtypes was: 67 GT1a (75.3%), 18 GT1b (20.2%), 1 GT1e (1.1%), and 3 GT4r (3.4%).

The prevalence of baseline polymorphisms at the key subset of amino acid positions 155, 156, or 168 in NS3, or 24, 28, 30, 31, 58, 92, or 93 in NS5A at the 15% NGS detection threshold was 15.9% (7/44) in NS3 and 65.9% (29/44) in NS5A among subjects in Arm D, and 17.8% (8/45) in NS3 and 61.4% (27/44) in NS5A among subjects in Arm E. Within each arm, the same percentage of subjects (29.5%, 13/44) had no baseline polymorphisms in either target, with many of these subjects (9 in Arm D and 6 in Arm E) belonging to the PI-experienced/NS5A-naïve previous regimen category.

The impact of baseline polymorphisms on treatment outcome was assessed. Among PI-experienced/NS5A-naïve subjects, the presence of baseline polymorphisms in NS3 and/or NS5A had no impact on treatment outcome, as all of these subjects achieved SVR<sub>12</sub>. Baseline NS5A polymorphisms were highly prevalent among NS5A-experienced subjects (80.6%, 50/62), whether the previous treatment was with an NS5A inhibitor alone or an NS5A inhibitor with a PI. Among the subjects in the NS5A-experienced/PI-naïve category who had baseline NS5A polymorphisms, 86.7% (13/15) of those in Arm D and 91.7% (11/12) in Arm E achieved SVR<sub>12</sub>. Among PI-naïve subjects, there were no subjects with polymorphisms in NS3, and there were no virologic failures among subjects without any baseline polymorphisms. Among NS5A-experienced/PI-experienced subjects, 71.4% (5/7) of subjects with baseline NS5A polymorphisms alone in Arm D achieved SVR<sub>12</sub>, while all subjects (8/8) with NS5A polymorphisms alone in Arm E achieved SVR<sub>12</sub>. In subjects experienced to both classes of inhibitors and with polymorphisms in both targets, lower SVR<sub>12</sub> rates (75.0%, 3/4 in Arm D, and 25%, 1/4 in Arm E) were seen compared with subjects with NS3 alone, NS5A alone, or no polymorphisms (80%, 8/10 in Arm D, and 100%, 12/12 in Arm E). Although the virologic failure rate across both treatment arms was higher in subjects with multiple baseline polymorphisms in NS5A or across both targets than in those with single NS5A or no polymorphisms, the combination of polymorphisms seen from subject to subject did not show a pattern predictive of virologic failure.

**Summary/Conclusions (Continued)**

**Pharmacokinetic Results:**

In subjects without cirrhosis at the ABT-493 300 mg + ABT-530 120 mg dose level, ABT-493 pharmacokinetic exposures resulting from administration of 100 mg tablets were comparable to the exposures resulting from administration of ABT-493/ABT-530 coformulated tablets. ABT-493 exposures were higher in subjects with cirrhosis compared to subjects without cirrhosis.

In subjects without cirrhosis at the ABT-493 300 mg + ABT-530 120 mg dose level, ABT-530 pharmacokinetic exposures resulting from administration of 40 mg tablets were comparable to the exposures resulting from administration of ABT-493/ABT-530 coformulated tablets. ABT-530 exposures in subjects with cirrhosis were comparable to subjects without cirrhosis.

**Safety Results:**

**Part 1:**

In Part 1, the percentage of subjects with AEs did not increase with the doses of ABT-493 and ABT-530 tested. The majority of subjects with AEs experienced events with a maximum severity of Grade 1 (mild), with the most common ( $\geq 10.0\%$  of subjects) being headache, fatigue, arthralgia, and nausea in the RBV-free arms and fatigue, nausea, insomnia, headache, nasopharyngitis, dyspnea, and pruritus among subjects in the RBV-containing arm. No subject had an AE leading to premature study drug discontinuation. Serious adverse events (SAEs) were rare (2 subjects each experienced 1 SAE) and considered not related to DAA treatment or RBV. There were no treatment-emergent AEs leading to death; 1 subject (Arm C) died during the follow-up period due to a non-treatment-emergent AE of metastatic hepatocellular cancer, an event considered not related to DAA treatment. No clinically meaningful observations were noted for hematology, clinical chemistry, urinalysis, vital signs, or 12-lead electrocardiogram assessments. No Grade 3 ALT elevations were observed. No subjects had a potential case of hepatotoxicity or experienced an event of hepatic decompensation/hepatic failure.

**Part 2:**

In Part 2, the percentage of subjects with AEs was similar among subjects treated for 12 weeks and 16 weeks. The majority of subjects with AEs experienced events with a maximum severity of Grade 1 (mild), with the most common ( $\geq 10.0\%$  of subjects) being headache in the 12-week arm and headache and fatigue in the 16-week arm. No subject had an AE leading to premature study drug discontinuation, and serious AEs were rare (3 subjects) and considered not related to DAA treatment. No subject died. Two subjects experienced nontreatment-emergent SAEs with diagnosis of hepatocellular carcinoma or hepatic cancer; both achieved SVR<sub>12</sub>. No clinically meaningful observations were noted for hematology, clinical chemistry, urinalysis, vital signs, or 12-lead electrocardiogram assessments. No Grade 3 ALT elevations were observed. No subjects had a potential case of hepatotoxicity or experienced an event of hepatic decompensation/hepatic failure.

No safety signals were observed in this study.

**Summary/Conclusions (Continued)**

**Conclusions:**

**Part 1:**

The combination of ABT-493 and ABT-530 achieved an SVR<sub>12</sub> rate of  $\geq 86.4\%$ , was well tolerated and demonstrated a favorable safety profile, with mostly mild AEs, no study drug-related SAEs, rare occurrences of clinically significant laboratory abnormalities, and no premature discontinuations of study drug due to AEs.

**Part 2:**

In subjects with and without cirrhosis who previously failed DAA-containing regimens, which included an NS5A inhibitor and/or PI, treatment with ABT-493/ABT-530 300 mg/120 mg demonstrated high efficacy, achieving up to 91.5% SVR<sub>12</sub> (in the 16-week arm).

Differences in efficacy were observed based on the type of treatment that subjects had failed prior to enrolling into the study:

- For subjects who were PI-experienced (NS5A-naïve), treatment with ABT-493/ABT-530 for either 12 or 16 weeks duration achieved 100% SVR<sub>12</sub>. Prior treatment history with PIs only or the presence of NS3 polymorphisms without NS5A polymorphisms did not affect efficacy. These efficacy results and the resistance profile of ABT-493 suggest that PI-experienced (NS5A-naïve) subjects could be effectively treated with the same regimen as those who are experienced with interferon with sofosbuvir and/or ribavirin.
- The 16-week duration resulted in a higher SVR<sub>12</sub> rate and a lower relapse rate than the 12-week duration in NS5A-experienced subjects, regardless of whether NS5A baseline polymorphisms were present.
- For subjects who had a previous treatment regimen containing only an NS5A inhibitor (without PI), treatment with ABT-493/ABT-530 for 16 weeks maximizes the SVR<sub>12</sub> rate (94.4% [17/18]).
- Lower efficacy was observed in subjects who were experienced with both PIs and NS5A inhibitors (81.3% [13/16] Arm E [16 weeks]). The lower efficacy in this subpopulation appeared to be driven by the presence of substitutions at the key subset of amino acid positions in both NS3 and NS5A targets at baseline.
- Baseline resistance testing is not likely to add substantial value to prior treatment history in predicting response to treatment in patients who have failed either an NS5A or a PI. In those who have failed both a PI and NS5A, the small minority of subjects with key substitutions in both targets had lower SVR<sub>12</sub> rates and would likely benefit from a more intensive regimen (i.e., adding a DAA with a different mechanism of action).

The combination of ABT-493/ABT-530 was well tolerated and demonstrated a favorable safety profile, with mostly mild AEs, no study drug-related SAEs, rare occurrences of clinically significant laboratory abnormalities, and no premature discontinuations of study drug due to AEs.

**Summary/Conclusions (Continued)**

**Conclusions (Continued):**

**Pharmacokinetics (Parts 1 and 2)**

- In subjects without cirrhosis at the ABT-493 300 mg + ABT-530 120 mg dose level, ABT-493 pharmacokinetic exposures resulting from administration of 100 mg tablets were comparable to the exposures resulting from administration of ABT-493/ABT-530 coformulated tablets. ABT-493 exposures were higher in subjects with cirrhosis compared to subjects without cirrhosis.
- In subjects without cirrhosis at the ABT-493 300 mg + ABT-530 120 mg dose level, ABT-530 pharmacokinetic exposures resulting from administration of 40 mg tablets were comparable to the exposures resulting from administration of ABT-493/ABT-530 coformulated tablets. ABT-530 exposures in subjects with cirrhosis were comparable to subjects without cirrhosis.