

Objectives:

The primary objectives 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, 4, 5 and 6 infection with compensated cirrhosis (GT1 only) or without cirrhosis (GT1, GT4, GT5, or GT6).

The secondary objectives were to assess the pharmacokinetics of ABT-493, ABT-530, and RBV, and the emergence and persistence of viral variants with this treatment regimen.

Note that although RBV was initially planned in the protocol, it was not administered in any of the study arms.

Methodology:

This was a Phase 2, open-label, multicenter, 2-part study to evaluate the efficacy, safety, and pharmacokinetics of co-administration of ABT-493 and ABT-530 in chronic HCV GT1-, GT4-, GT5-, and GT6-infected subjects with compensated cirrhosis (GT1 only) or without cirrhosis (GT1, GT4, GT5, or GT6). Part 1 enrolled subjects who received ABT-493 and ABT-530 for 12 weeks. Part 2 enrolled subjects who received ABT-493 and ABT-530 for 8 or 12 weeks. Subjects who completed or prematurely discontinued the Treatment Period were followed for 24 weeks to monitor HCV RNA to evaluate efficacy and the emergence and persistence of viral variants.

For Part 1, approximately 80 GT1 treatment-naïve (TN) or pegIFN/RBV (PR)-null responder subjects without cirrhosis were enrolled sequentially into one of 2 treatment arms (40 subjects planned per arm):

Arm A: ABT-493 200 mg once daily (QD) + ABT-530 120 mg QD for 12 weeks

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

Part 2 of the study was initiated based on evaluation of efficacy and safety results from Part 1, as follows:

Genotype 1-infected TN or PR-experienced subjects without cirrhosis were enrolled into Arm K.

Genotype 1-infected TN or PR-experienced subjects with compensated cirrhosis were enrolled into

Arm F. Genotype 4-, GT5-, and GT6-infected TN or PR-experienced subjects without cirrhosis were enrolled into Arm I.

The regimens corresponding to each of those arms (30 subjects planned per arm) were:

Arm K: ABT-493 300 mg QD + ABT-530 120 mg QD for 8 weeks

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

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

Post-treatment relapse, defined as HCV RNA < lower limit of quantitation (LLOQ) at the end of treatment with a confirmed HCV RNA \geq LLOQ (defined as 2 consecutive HCV RNA measurements \geq LLOQ) in the Post-Treatment Period, was monitored throughout the study to determine if the treatment duration was optimal. Within each arm, if the proportion of subjects with relapse had exceeded 10% of subjects who completed the assigned therapy (minimum of 10 subjects who completed treatment as assigned evaluated), all remaining subjects or a subset of subjects (e.g., treatment-experienced) enrolled in the same or the related arm who had not reached the end of assigned treatment, would have been offered an additional 4 weeks of study drug treatment.

Number of Subjects (Planned and Analyzed):

Planned: up to 350 subjects (approximately 80 subjects in Part 1; approximately 270 subjects in Part 2).

Analyzed: 174 subjects (79 in Part 1 and 95 in Part 2) were enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria:

1. Male or female (of non-child bearing potential, sexually active with female partners only, or using approved contraceptive methods) and age between 18 and 70 years of age, inclusive, at time of Screening.
2. Screening laboratory result indicating HCV GT1 (Parts 1 and 2) or HCV GT4, GT5, or GT6 (Part 2) infection.
3. Chronic HCV infection defined as one of the following:
 - Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or
 - Positive for anti-HCV Ab 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).
4. Subject had to meet one of the following criteria:
 - Treatment-naïve: subject had never received treatment for HCV infection.
 - Treatment-experienced: PR-null responder (for Part 1) or PR-experienced (on-treatment failure or prior relapse) (for Part 2).
5. Documented absence of cirrhosis (in Part 1 and in corresponding arms of Part 2), or compensated cirrhosis (in corresponding arms of Part 2, GT1 only), per local standard.

Main Exclusion Criteria:

1. History of severe, life-threatening or other significant sensitivity to any drug.
2. Positive test result for hepatitis B surface antigen (HBsAg) or anti-human immunodeficiency virus antibody (HIV Ab).
3. Hepatitis C virus genotype performed during screening indicating co-infection with more than one HCV genotype.
4. Any cause of liver disease other than chronic HCV-infection.
5. Subjects with plasma HCV RNA load \leq 10,000 IU/mL or unquantifiable or undetectable HCV RNA at Screening.
6. Previous use of an HCV direct-acting antiviral agent (DAA).
7. Consideration by the investigator, for any reason, that the subject was an unsuitable candidate to receive ABT-493, ABT-530, or RBV (RBV for cirrhotic subjects only).
8. For subjects in Part 2 who were enrolling with compensated 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 exam), bleeding varices, use of beta-blockers 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	AbbVie	100 mg tablet/Oral	14-001033 14-001291
ABT-530	AbbVie	40 mg tablet/Oral	14-001596 14-002134
Duration of Treatment:			
Subjects in Part 1 were to receive ABT-493 and ABT-530 for 12 weeks. Subjects in Part 2 were to receive ABT-493 and ABT-530 for 8 or 12 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 sustained virologic response 12 weeks post dosing (SVR ₁₂) and who had a post-baseline sample with HCV RNA \geq 1000 IU/mL: 1) the amino acid variants in available post-baseline samples identified by population, deep or clonal nucleotide sequencing and comparison to the baseline sequence, 2) the amino acid variants in available post-baseline 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, deep or clonal nucleotide sequencing.			
Patient-Reported Outcomes:			
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 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:			
Individual plasma concentrations of ABT-493 and ABT-530 were summarized.			
Safety:			
Safety and tolerability was assessed by monitoring adverse events (AEs), physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECGs), and vital signs.			

Statistical Methods

Efficacy:

The primary endpoint was the percentage of subjects who achieved SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). For each treatment arm, the number and percentage of subjects achieving SVR₁₂ were summarized along with a 95% confidence interval (CI) using Wilson score interval.

The secondary endpoints were:

- The percentage of subjects with SVR₄ (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 LLOQ after HCV RNA < LLOQ during treatment, confirmed increase of $> 1 \log_{10}$ 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 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).

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

The following additional efficacy endpoints were summarized descriptively by treatment arm:

- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using data as observed);
- The percentage of subjects who achieved SVR₂₄;
- The percentage of subjects who relapsed after achieving SVR₁₂.

Resistance:

The following resistance information was analyzed for baseline samples from subjects: 1) the variants at signature resistance-associated amino acid position at baseline identified by population sequencing or next-generation sequencing (NGS) were compared to the appropriate prototypic reference sequence; and, (2) For subjects in Arms A, B and F, comparison of SVR₁₂ rates in subjects with or without baseline variants was conducted.

The following resistance information was analyzed for subjects receiving combination therapy who did not achieve SVR and had HCV RNA \geq 1000 IU/mL: 1) the variants at available post-baseline time points identified by population nucleotide sequencing were compared to baseline sequences, 2) the most prevalent amino acid variants found by population sequencing and amino acid variants that emerged or became enriched in isolates from at least 2 subjects of the same subgenotype, and 3) the persistence of variants at resistance-associated amino acid positions.

HCV Genotype/Subtype:

Phylogenetic analysis was conducted on all available HCV sequences from baseline sample obtained from each subject infected with GT1, GT4, GT5, or GT6 HCV in order to accurately determine its subtype.

Patient-Reported Outcomes:

Changes from baseline in the patient reported outcome summary measures, other than HCVTsat, were summarized descriptively. Treatment satisfaction was measured by the HCVTsat at Post-Treatment Week 4 and summarized descriptively.

Statistical Methods (Continued)

Pharmacokinetics:

Individual plasma concentrations of ABT-493 and ABT-530 were tabulated for each subject and group at visits with intensive pharmacokinetic sample collections (Day 1 and Week 4). Results were tabulated for each subject and summary statistics were computed for each sampling time within each arm.

Individual plasma concentrations of ABT-493 and ABT-530 for visits after Week 1 were summarized.

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. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA[®]). The number and percentage of subjects with treatment-emergent adverse events (TEAEs, i.e., event that began or worsened in severity after initiation of study drug through 30 days post-study drug dosing) were tabulated by primary System Organ Class (SOC) and preferred term. The number of subjects with TEAEs by grade (CTCAE Grades 1 – 5) and relationship to study drug was also provided. Mean changes from baseline in laboratory tests and vital signs to each post-baseline visit were summarized, as were the number and percentage of subjects with on-treatment laboratory abnormalities by toxicity grade and the number and percentage of subjects with post-baseline values meeting pre-defined criteria for potentially clinically significant vital signs.

Summary/Conclusions

Efficacy Results:

SVR₁₂ rates were greater than 95% in all treatment arms, regardless of baseline characteristics such as HCV genotype, fibrosis stage (including compensated cirrhosis), as shown in the table below, or previous HCV treatment history.

Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR₁₂) (ITT Population)

Assessment	Part 1		Part 2		
	GT1-Infected		GT1-Infected		GT4-, GT5-, or GT6-Infected
	No Cirrhosis		No Cirrhosis	Compensated Cirrhosis	No Cirrhosis
	Arm A 200 mg/ 120 mg ^a QD × 12 wks	Arm B 200 mg/ 40 mg ^a QD × 12 wks	Arm K 300 mg/ 120 mg ^a QD × 8 wks	Arm F 200 mg/ 120 mg ^a QD × 12 wks	Arm I 300 mg/ 120 mg ^a QD × 12 wks
SVR ₁₂ , n/N (%)	40/40 (100)	38/39 (97.4)	33/34 (97.1)	26/27 (96.3)	34/34 (100)
95% CI ^b	91.2, 100	86.8, 99.5	85.1, 99.5	81.7, 99.3	89.8, 100
Nonresponders ^c , n/N (%)	0/40	1/39 (2.6)	1/34 (2.9)	1/27 (3.7)	0/34 (0)
Reason for nonresponse, n/N (%)					
Virologic failure	0/40	1/39 (2.6)	0/34	1/27 (3.7)	0/34
On-treatment virologic failure	0/40	0/39	0/34	0/27	0/34
Relapse	0/40	1/38 (2.6)	0/33	1/27 (3.7)	0/34
Non-virologic failure	0/40	0/39	1/34 (2.9)	0/27	0/34
Premature study drug discontinuation	0/40	0/39	1/34 (2.9)	0/27	0/34
Missing SVR ₁₂ data	0/40	0/39	0/34	0/27	0/34
Other	0/40	0/39	0/34	0/27	0/34

CI = confidence interval; ITT = intent-to-treat; SVR₁₂ = sustained virologic response 12 weeks post dosing

- a. Doses of ABT-493 and ABT-530, respectively.
- b. Confidence interval constructed using the Wilson score method.
- c. Did not achieve SVR₁₂ for any reason.

Note: Backward imputation, where applicable, was to be used to impute missing data; after applying backward imputations, subjects with missing data were counted as failures.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

All 174 subjects achieved HCV RNA < LLOQ at their final treatment visit, 171 (98.3%) subjects achieved SVR₁₂, and 3 subjects were SVR₁₂ non-responders, including 2 relapses at Post-Treatment Week 4 and 1 premature discontinuation on Treatment Day 29 due to an AE of adenocarcinoma (subject achieved SVR₄ but died prior to the Post-Treatment Week 12 visit). Among GT1-infected subjects without cirrhosis, there was no meaningful difference in SVR₁₂ rate between the 12-week (Arms A and B) and 8-week (Arm K) regimens.

Among 107 GT1-, GT4-, GT5-, and GT6-infected subjects without cirrhosis receiving either 200 mg or 300 mg of ABT-493 and 120 mg of ABT-530, no subject experienced relapse. In the same subject population among those who received the lowest dose combination of ABT-493 200 mg and ABT-530 40 mg, 1 subject (of 38, Arm B) experienced relapse. Among GT1-infected subjects with compensated cirrhosis who received 200 mg/120 mg for 12 weeks, 1 subject (of 27, Arm F) experienced relapse.

Of the 171 subjects who achieved SVR₁₂, 168 subjects with available HCV RNA data also achieved SVR₂₄. There were no observed relapses between SVR₁₂ and SVR₂₄.

By Week 2, HCV RNA < LLOQ was observed in the majority of subjects (83.3%) across treatment arms and for all subjects but 1 by Week 4.

Resistance Results:

Phylogenetic analysis of HCV nonstructural viral protein 3/4A (NS3/4A) and nonstructural viral protein 5A (NS5A) sequences from subjects in Arm I identified 11 HCV subtypes (18 4a, 2 4d, 1 4g/4k, 1 4o, 1 5a, 2 6a, 4 6e, 1 6h, 1 6p, 1 6q, and 2 6r).

Baseline polymorphisms were commonly observed at signature amino acid positions in NS3/4A (43.0%, 74/172) and NS5A (20.9%, 36/172), but they had no impact on response to treatment in any arm of the study. Two GT1a-infected subjects experienced virologic failure. At the time of failure, both had treatment-emergent NS5A variants, but neither had treatment-emergent NS3/4A variants at resistance-associated amino acid positions. The NS5A variants persisted through Post-Treatment Week 24 in both subjects.

Pharmacokinetic Results:

Both ABT-493 and ABT-530 exposures increased in a dose-dependent manner in HCV infected subjects. ABT-493 exposures were higher in subjects with compensated cirrhosis compared to subjects without cirrhosis. ABT-530 exposures were similar in subjects with compensated cirrhosis and subjects without cirrhosis.

Safety Results:

The ABT-493 and ABT-530 regimens were well-tolerated, demonstrating a favorable safety profile. No dose-dependent AEs were identified. The safety profile of the ABT-493 and ABT-530 regimen observed in subjects with compensated cirrhosis (Arm F) was similar to that of subjects without cirrhosis (Arm A) at the same dose levels. Most TEAEs were mild in severity. No treatment-related serious adverse events and no treatment-related AEs leading to treatment discontinuation were reported.

Two subjects died, 1 due to a TEAE of adenocarcinoma (after having discontinued study drug prematurely due to the event) and 1 due to a non TEAE of completed suicide; both events leading to death were considered to have no reasonable possibility of being related to the study drug.

Summary/Conclusions (Continued)					
Overview of Adverse Events – Parts 1 and 2 (Safety Population)					
	Number (%) of Subjects				
	Part 1		Part 2		
	GT1-Infected		GT1-Infected		GT4-, GT5-, or GT6-Infected
	No Cirrhosis		No Cirrhosis	Compensated Cirrhosis	No Cirrhosis
Type of Adverse Event	Arm A 200 mg/ 120 mg^a QD × 12 wks N = 42	Arm B 200 mg/ 40 mg^a QD × 12 wks N = 39	Arm K 300 mg/ 120 mg^a QD × 8 wks N = 34	Arm F 200 mg/ 120 mg^a QD × 12 wks N = 27	Arm I 300 mg/ 120 mg^a QD × 12 wks N = 32
Any TEAE	26 (61.9)	30 (76.9)	23 (67.6)	14 (51.9)	23 (71.9)
Serious TEAEs	1 (2.4)	0	1 (2.9)	1 (3.7)	0
TEAEs leading to discontinuation of study drug	0	0	1 (2.9)	0	0
TEAEs leading to death	0	0	1 (2.9)	0	0
All deaths ^b	1 (2.4)	0	1 (2.9)	0	0

TEAE = treatment-emergent adverse event

a. Dose of ABT-493 and ABT-530, respectively.

b. Includes non-treatment emergent deaths.

Note: Two subjects assigned to Arm I received ABT-493 200 mg QD + ABT-530 120 mg QD for 12 weeks and are therefore included in Arm A instead of Arm I.

No clinically meaningful observations were noted for hematology, clinical chemistry, urinalysis, vital signs, or ECG assessments. None of the subjects had liver function test values that met the criteria for Hy's law.

No safety signals were observed in this study.

Summary/Conclusions (Continued)

Conclusions:

- SVR₁₂ rates were greater than 95% in all treatment arms of subjects with chronic HCV GT1, GT4, GT5, or GT6 infection following treatment with ABT-493 and ABT-530 for 8 or 12 week, regardless of baseline characteristics such as HCV genotype, fibrosis stage (including compensated cirrhosis), or previous HCV treatment history.
- Among GT1-infected subjects without cirrhosis, duration of treatment longer than 8 weeks did not increase efficacy.
- Among GT1-infected subjects with compensated cirrhosis, the low rate of relapse suggests that a 12-week duration of treatment is appropriate.
- The highest doses of 300 mg and 120 mg of ABT-493 and ABT-530, respectively, appear to be the most effective doses, preventing the occurrence of relapse. Both subjects who relapsed were treated with regimens containing doses of ABT-493/ABT-530 lower than the dose selected for evaluation in Phase 3 (300 mg/120 mg).
- No subjects relapsed after achieving SVR₁₂.
- Baseline polymorphisms at signature amino acid positions were commonly observed in NS3/4A and NS5A, but they did not impact response.
- Both ABT-493 and ABT-530 exposures increased in a dose-dependent manner in HCV-infected subjects. ABT-493 exposures were higher in subjects with compensated cirrhosis compared to subjects without cirrhosis. ABT-530 exposures were similar in subjects with compensated cirrhosis and subjects without cirrhosis.
- The ABT-493 and ABT-530 regimens were well-tolerated, demonstrating a favorable safety profile.
- No dose-dependent AEs were identified.
- The safety profile of the ABT-493 and ABT-530 regimen observed in subjects with compensated cirrhosis (Arm F) was similar to that of subjects without cirrhosis (Arm A) at the same dose levels.
- No safety signals were observed in this study.