



**Objectives:**

The primary objectives of this study were to evaluate the effect of response to treatment by evaluating the percentage of subjects achieving a 12-week sustained virologic response (SVR<sub>12</sub>) of 12 weeks of treatment with ABT-493/ABT-530 and to evaluate safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus (HCV) genotype (GT) 4, 5, or 6 infection.

The secondary objectives were to assess the percentage of subjects with on-treatment virologic failure and post-treatment relapse.

Additional objectives were to assess pharmacokinetics and emergence and persistence of viral variants in this treatment regimen.

**Methodology:**

Study M13-583 was a Phase 3, single arm, open-label, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in HCV GT4-, GT5-, or GT6-infected subjects without cirrhosis, who were either HCV treatment-naïve or treatment-experienced (i.e., had failed prior interferon [IFN] ± ribavirin [RBV], pegylated interferon [pegIFN] ± RBV, or sofosbuvir [SOF] + RBV ± pegIFN). The study consisted of a Screening Period, Treatment Period, and Post-Treatment Period. 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 post-treatment to monitor for safety, HCV RNA, and the emergence and/or persistence of resistance-associated viral variants.

The planned total duration of the study (excluding screening) was up to 36 weeks for all subjects.

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

Planned: Approximately 130 subjects

Analyzed: 121 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 nonchildbearing potential, practicing total abstinence, sexually active with female partners only, or using allowed contraceptive methods) at least 18 years of age at time of screening.
- Screening laboratory result indicating HCV GT4, 5, or 6 infection.
- 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, or
  - Abnormal alanine aminotransferase levels for at least 6 months before screening.
- Hepatitis C virus treatment-naïve or had failed prior IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN therapy. Prior HCV treatment with any other approved or investigational medications was not allowed.
- Documented as noncirrhotic.

**Main Exclusion Criteria:**

- 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.

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

**Main Exclusion Criteria (Continued):**

- 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 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.
- 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 coformulation	AbbVie	Oral	Tablet	100 mg/ 40 mg	15-005116, 15-006020

**Duration of Treatment:**

Subjects received ABT-493/ABT-530 300 mg/120 mg once daily (QD) for 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 in available samples at signature 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 prototypic reference sequences were analyzed. The following resistance information was analyzed for subjects receiving active study drug 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 NGS and comparison to the baseline sequences, 2) the amino acid variants in available postbaseline samples at signature resistance-associated positions identified by NGS and comparison to the appropriate prototypic reference sequences, and 3) the persistence of viral resistance by NGS.

**Criteria for Evaluation (Continued)****Patient Reported Outcomes (PROs):**

Health state utility was measured using the EuroQol-5 Dimensions-3 Level instrument. The Work Productivity and Activity Impairment Questionnaire: Hepatitis C assessed work and activity impairment due to HCV. The Fatigue Severity Scale was used to measure the severity of fatigue and its effect on lifestyle and activities. The Short Form 36-Version 2 Health Status Survey was used to assess the functional health and well-being of subjects.

**Pharmacokinetics:**

Plasma concentrations and pharmacokinetic parameter values for ABT-493 and ABT-530 were tabulated. Summary statistics were computed for each time on intensive pharmacokinetic collection 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 variable was SVR<sub>12</sub>, defined as HCV RNA < lower limit of quantitation (LLOQ) 12 weeks after the last actual dose of study drug. The number and percentage of subjects in the intention-to-treat (ITT) population achieving SVR<sub>12</sub> were summarized with a 2-sided 95% confidence interval (CI), calculated using the normal approximation to the binomial distribution. If the SVR<sub>12</sub> rate was 100%, then the Wilson's score method was used to calculate the CI.

The secondary efficacy endpoints were:

- The percentage of subjects with on-treatment virologic failure (defined as confirmed increase of > 1 log<sub>10</sub> IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ 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 ≥ 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).

The percentage of subjects meeting each secondary efficacy endpoint was summarized with 2-sided 95% Wilson score intervals.

**Resistance:**

The genes of interest for NGS in this study in all samples were those encoding full length nonstructural viral protein 3/4A 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.

**HCV Genotype/Subtype:**

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

**Statistical Methods (Continued)****Subgroup:**

The percentage of subjects with SVR<sub>12</sub> and with Relapse<sub>12</sub> was calculated, along with the corresponding 2-sided 95% Wilson score intervals, for subgroup variables such as HCV GT subtype (4, 5, or 6), prior HCV treatment history, interleukin 28B genotype, and baseline HCV RNA level.

**Pharmacokinetics:**

Individual plasma concentrations of ABT-493 and ABT-530 were tabulated for each subject. Summary statistics were computed for each time on intensive pharmacokinetic collection days.

**Safety:**

All subjects who received at least 1 dose of study drug were included in the safety analyses. 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 treatment-emergent AEs by severity grade (Grades 1 – 5) and relationship to study drug was also provided.

Mean changes in clinical laboratory and vital sign data from baseline to each postbaseline visit were summarized descriptively. The number and percentage of subjects with postbaseline values meeting potential hepatotoxicity criteria were summarized. The number and percentage of subjects with postbaseline values during the treatment period meeting prespecified criteria for potentially clinically significant laboratory or vital sign values or toxicity grades were summarized.

**Summary/Conclusions****Efficacy Results:**

Sustained virologic response 12 weeks postdosing was achieved by 99.2% (120/121) of subjects treated with ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks in the ITT population. No subjects experienced on-treatment virologic failure or post-treatment relapse.

**Summary/Conclusions (Continued)**

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

Assessment	ABT-493/ABT-530 (N = 121) n/N (%)
SVR <sub>12</sub> , n/N (%)	120/121 (99.2)
95% CI	97.6, 100.0
Nonresponse, n/N (%)	1/121 (0.8)
Reason for nonresponse, n/N (%)	
Virologic failure	0/121
On-treatment virologic failure	0/121
Relapse	0/118
Non-virologic failure	1/121 (0.8)
Premature study drug discontinuation	1/121 (0.8)
HCV reinfection	0/121
Missing SVR <sub>12</sub> data	0/121
Other	0/121

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

CI = confidence interval; 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

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 value from a local laboratory present, then it was to be imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.

**Resistance Results:**

Based on phylogenetic analysis of NS3/4A or NS5A sequences from 110 subjects, 8 GT4 subtypes, 1 GT5 subtype, and 5 GT6 subtypes were identified in the study, broken down into 26 GT4a, 36 GT4d, 1 GT4f, 1 GT4g, 4 GT4k, 1 GT4m, 1 GT4o, 3 GT4r, 26 GT5a, 5 GT6a, 3 GT6e, 1 GT6p, 1 GT6q, and 1 GT6r.

Baseline polymorphisms at the key subset of amino acid positions in NS3 (positions 155, 156, or 168) were not detected in GT4-infected subjects, and were detected in 46.2% (12/26) and 9.1% (1/11) of the GT5a- and GT6-infected subjects, respectively. NS5A polymorphisms (at positions 24, 28, 30, 31, 58, 92, or 93) were detected in 61.1% (44/72), 15.4% (4/26), and 63.6% (7/11) of the GT4-, GT5a-, and GT6-infected subjects, respectively. The presence of baseline polymorphisms had no impact on treatment outcome in subjects infected with any HCV subtype in this study, as no subject in the mITT-GT-VF population experienced virologic failure.

**Summary/Conclusions (Continued)****Pharmacokinetic Results:**

Following administration of ABT-493/ABT-530 300 mg/120 mg QD, ABT-493 and ABT-530 plasma concentrations attained steady state by the Week 1 Visit. ABT-493 and ABT-530 concentrations remained constant throughout the treatment period, with no apparent drug accumulation observed. Maximum ABT-493 and ABT-530 concentrations were reached at approximately 4 hours postdosing.

**Safety Results:**

The fixed-dose combination of ABT-493/ABT-530 300 mg/120 mg QD administered for 12 weeks was well tolerated, demonstrating a favorable safety profile. The majority of subjects who experienced AEs had events that were at most Grade 1 (mild) in severity, with the most common ( $\geq 10.0\%$  of subjects) being headache and fatigue. Serious adverse events and AEs leading to discontinuation of study drug were rare. Laboratory abnormalities were infrequent and not clinically significant. No subjects experienced events of hepatic decompensation and there were no suspected cases of drug-induced liver injury.

**Conclusions:**

- Subjects without cirrhosis infected with HCV GT4 – GT6 who were treated for 12 weeks with ABT-493/ABT-530 300 mg/120 mg QD achieved an SVR<sub>12</sub> rate of 99.2%, with no virologic failures.
- High SVR<sub>12</sub> rates were observed in HCV GT4-6-infected subjects without cirrhosis, regardless of viral or host factors, including demographics, baseline HCV RNA levels, HCV genotype, relevant comorbidities, prior treatment history, or presence of baseline polymorphisms in NS3 and/or NS5A.
- Following administration of ABT-493/ABT-530 300 mg/120 mg QD, ABT-493 and ABT-530 plasma concentrations attained steady state by the Week 1 Visit. ABT-493 and ABT-530 concentrations remained constant throughout the treatment period, with no apparent drug accumulation observed. Maximum ABT-493 and ABT-530 concentrations were reached at approximately 4 hours postdosing.
- The fixed-dose combination of ABT-493/ABT-530 300 mg/120 mg QD administered for 12 weeks was well tolerated, demonstrating a favorable safety profile.