2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-493/ABT-530		
Name of Active Ingredient: **ABT-493:** (3a*R*,7*S*,10*S*,12*R*,21*E*,24a*R*)-7-*tert*-butyl-*N*-{(1*R*,2*R*)-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-1*H*,10*H*-9,12-methanocyclopenta[18,19][1,10,17,3,6]trioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide hydrate **ABT-530:** 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		
Title of Study: A Randomized, Double-Blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 2 Infection (ENDURANCE-2)		
Coordinating Investigator: [redacted]		
Study Sites: 55 sites in Belgium, France, Italy, Korea, Lithuania, Portugal, Taiwan, and the United States		
Publications: 1 abstract		
Studied Period (Years): First Subject First Visit: 27 November 2015 Last Subject Last Visit for Primary Analysis: 09 September 2016	**Phase of Development:** 3	

Objectives:

The primary objectives were to assess the efficacy (sustained virologic response 12 weeks post dosing [SVR_{12}]) of treatment with the ABT-493/ABT-530 combination regimen compared to a historical SVR_{12} rate of treatment with sofosbuvir (SOF) + ribavirin (RBV) and to assess the safety of 12 weeks of treatment with the ABT-493/ABT-530 combination regimen compared to placebo in adults with chronic hepatitis C virus (HCV) genotype (GT) 2 infection without underlying cirrhosis.

The secondary objectives were to assess the percentage of subjects treated with the ABT-493/ABT-530 combination regimen with on-treatment virologic failure during the Double-Blind (DB) Treatment Period, to assess the percentage of subjects treated with the ABT-493/ABT-530 combination regimen with post-treatment relapse following the DB Treatment Period, and to assess the efficacy (SVR_{12}) of treatment with the ABT-493/ABT-530 combination among subjects with prior SOF + RBV ± pegylated-interferon alfa-2a or alfa-2b (pegIFN) failure.

Methodology:

This was a Phase 3, randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 in HCV GT2-infected subjects without cirrhosis, who were either HCV treatment-naïve or prior treatment-experienced (i.e., with interferon [IFN] or pegIFN ± RBV or SOF + RBV ± pegIFN).

Chronic HCV GT2-infected adults without underlying cirrhosis meeting all eligibility criteria were randomized in a 2:1 ratio into Arm A or Arm B:

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

Arm B: Matching placebo QD for 12 weeks followed by open-label ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks

The study consisted of 3 periods:

DB Treatment Period: Subjects were randomized in a 2:1 ratio to receive either 12 weeks of ABT-493/ABT-530 (Arm A) or 12 weeks of matching placebo (Arm B), respectively.

Open-Label (OL) Treatment Period: Subjects randomized to placebo in the DB Treatment Period received open-label ABT-493/ABT-530 for 12 weeks.

Post-Treatment Period: Subjects randomized to active drug (Arm A) who completed or prematurely discontinued study drug during the DB Treatment Period and subjects randomized to placebo (Arm B) who completed the OL Treatment Period or prematurely discontinued study drug in the OL Treatment Period were followed for 24 weeks post-treatment to monitor HCV RNA levels and to evaluate safety, efficacy, and the emergence and persistence of resistant viral variants.

Randomization of subjects was stratified into 3 strata by type of previous treatment experience (i.e., HCV treatment-naïve or the last treatment regimen that the subject had received, either IFN or pegIFN ± RBV or SOF + RBV ± pegIFN). The prior SOF + RBV ± pegIFN subjects were analyzed separately for the primary and secondary endpoints.

During the DB Treatment Period, AbbVie, investigators, and subjects were blinded to drug assignment and virologic results. Virologic results were reviewed and virologic failure criteria applied by an unblinded, independent reviewer only to those subjects randomized to Arm A (ABT-493/ABT-530). Certain safety laboratory results which could potentially be unblinding (i.e., alanine aminotransferase, aspartate aminotransferase, total, direct, and indirect bilirubin) were also blinded to AbbVie, investigators, and subjects.

Methodology (Continued):

During the OL Treatment Period, study drug, virologic results, and safety laboratory results were not blinded. Virologic failure criteria were evaluated and applied by the investigator.

The planned total duration of the study (excluding screening) was up to 36 weeks for subjects in Arm A and 48 weeks for subjects in Arm B.

Number of Subjects (Planned and Analyzed):

Planned: approximately 291 to 321 subjects.

Analyzed: 304 subjects were randomized and 302 subjects 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) who was at least 18 years of age at time of screening.
- Screening laboratory result indicating HCV GT2 infection.
- Positive anti-HCV antibody (Ab) and plasma HCV RNA load ≥ 1,000 IU/mL at screening.
- Chronic HCV infection, defined as 1 of the following:
  - Positive for anti-HCV Ab or HCV RNA at least 6 months before screening, or
  - A liver biopsy consistent with chronic HCV infection, or
  - Abnormal alanine aminotransferase levels for > 6 months before screening.
- HCV treatment-naïve (subject had never received a single dose of any approved or investigational regimen) or had failed prior IFN or pegIFN ± RBV or SOF + RBV ± pegIFN therapy.
- 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.
- 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 Ab.
- HCV genotyping performed during screening indicated coinfection with more than 1 HCV genotype.
- Consideration by the investigator, for any reason, that the subject was an unsuitable candidate to receive ABT-493/ABT-530.
- Any cause of liver disease other than chronic HCV infection.
- History of severe, life-threatening, or other significant sensitivity to any excipient of the study drugs.

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

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
ABT-493/ABT-530	AbbVie	Oral	Tablet	100 mg/ 40 mg	15-004350, 15-005116

Duration of Treatment:

Subjects in Arm A received ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks. Subjects in Arm B received matching placebo QD for 12 weeks followed by open-label ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks.

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

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
Placebo for ABT-493/ABT-530	AbbVie	Oral	Tablet	0 mg	15-005142

Criteria for Evaluation

Efficacy:

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

Resistance:

For all subjects receiving ABT-493/ABT-530, the variants in available samples at signature amino acid positions at baseline identified by next-generation sequencing (NGS) and comparison to the appropriate prototypic reference sequence were analyzed. The following resistance information was to be analyzed for subjects receiving active study drug who did not achieve SVR_{12} and who had a postbaseline sample with HCV RNA ≥ 1,000 IU/mL: 1) the amino acid variants in available postbaseline samples identified by NGS, and comparison to the baseline sequence, 2) the amino acid variants in available postbaseline samples at signature positions identified by NGS and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral resistance by NGS.

Pharmacokinetics:

Plasma concentrations for ABT-493 and ABT-530 were tabulated for each subject in Arm A.

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 with SVR_{12} (HCV RNA < lower limit of quantitation [LLOQ] 12 weeks after the last actual dose of study drug) for the subjects treated with ABT-493/ABT-530 in the DB Treatment Period (Arm A), excluding prior SOF + RBV ± pegIFN failures. The percentage of these subjects treated with ABT-493/ABT-530 with SVR_{12} would be noninferior to the 95% SVR_{12} rate of the current standard-of-care (SOF + RBV for 12 weeks) if the lower confidence bound (LCB) of the 2-sided 95% confidence interval (CI) of the percentage of subjects with SVR_{12} was > 89%. The noninferiority margin of 6% was computed based on the historical SVR_{12} rates in HCV GT2-infected subjects. This noninferiority margin of 6% was chosen because it preserves 68% of the benefit of the SOF + RBV regimen over the previous pegIFN + RBV standard-of-care regimen.

The normal approximation to the binomial distribution was used to calculate the CIs unless the rate for the primary endpoint was 100%, in which case Wilson's score method was used instead.

In order to control the type 1 error rate, a fixed sequence testing procedure was used for the primary efficacy endpoint and the first secondary efficacy endpoint. Only if success was demonstrated for the primary endpoint (noninferiority of the SVR_{12} rate of Arm A to the historical control rate) did testing proceed to the first secondary endpoint (superiority of the SVR_{12} rate in Arm A to the historical control rate).

The secondary efficacy endpoint included in the fixed sequence testing procedure was superiority of the percentage of Arm A subjects treated with ABT-493/ABT-530, excluding prior SOF + RBV ± pegIFN failures, with SVR_{12} to the 95% SVR_{12} rate of the current standard-of-care (SOF + RBV for 12 weeks).

The percentage of these subjects treated with ABT-493/ABT-530 with SVR_{12} would be superior to the 95% SVR_{12} rate of the current standard of care (SOF + RBV for 12 weeks) if the LCB of the 2-sided 95% CI of the percentage of subjects with SVR_{12} was > 95%.

Other secondary efficacy endpoints not included in the fixed sequence testing procedure were:

- The percentage of subjects in Arm A, excluding prior SOF + RBV ± pegIFN failures, with on-treatment virologic failure (defined as confirmed increase of > 1 log_{10} IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA ≥ LLOQ at the end of treatment with at least 6 weeks of treatment) during the DB Treatment Period;
- The percentage of subjects in Arm A, excluding prior SOF + RBV ± pegIFN failures, 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 with HCV RNA < LLOQ at the end of treatment) following the DB Treatment Period;
- The percentage of subjects in Arm A with prior SOF + RBV ± pegIFN failure with SVR_{12}.

The percentage of subjects with on-treatment virologic failure, the percentage of subjects with post-treatment relapse, and the percentage of subjects with SVR_{12} among the prior SOF + RBV ± pegIFN failures were presented with 2-sided 95% CIs using Wilson's score method. These endpoints were not part of the fixed sequence testing procedure as no hypothesis was being tested.

For the analysis of relapse, completion of treatment was defined as any subject with study drug duration of 77 days or greater, regardless of treatment arm.

Statistical Methods (Continued)

Resistance:

The genes of interest for NGS in this study in all samples were those encoding full length nonstructural viral protein 3/4A and nonstructural viral protein 5A (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 nonstructural viral protein 3 (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.

Subgroup:

The percentage of subjects in Arm A of the DB Treatment Period, excluding prior SOF + RBV ± pegIFN failures, with SVR_{12} and with $Relapse_{12}$ were calculated, along with the corresponding 2-sided 95% Wilson score intervals, for subgroup variables such as HCV GT2 subtype, 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 in Arm A. Summary statistics were computed for each sampling time.

Safety:

All subjects who received at least 1 dose of study drug were included in the safety analyses. For safety analyses, data from the active (Arm A) and placebo (Arm B) treatment arms during the DB Treatment Period were summarized and comparisons of the 2 arms were performed. The number and percentage of subjects in each treatment arm 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 active study drug) were tabulated by primary Medical Dictionary for Regulatory Activities® 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, including applicable Post-Treatment Visits, were summarized and the mean change difference between the active and placebo arms at each visit in the DB Treatment Period were analyzed using an analysis of variance model with treatment group as the factor. Shift tables from baseline (categorized as low, normal or high) to minimum and maximum laboratory values (categorized as low, normal or high) during the DB Treatment Period, respectively, were created for each treatment arm. The number and percentage of subjects with postbaseline values meeting toxicity grades (Grades 1 – 4) and meeting potential hepatotoxicity criteria and with postbaseline values meeting predefined criteria for potentially clinically significant vital sign values were summarized. The differences in proportions of subjects with Grade 3/4 laboratory values during the DB Treatment Period and a 2-sided 95% CI were calculated between arms using Wilson's score method.

Summary/Conclusions

Efficacy Results:

SVR_{12} was achieved by 99.5% of subjects treated with ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks during the DB Treatment Period (Arm A of the intention-to-treat [ITT] population, excluding prior SOF + RBV ± pegIFN failures), with 2-sided 95% CI of 98.5% to 100.0%. The LCB of the 2-sided 95% CI was above 89% (noninferiority threshold). Therefore, the primary efficacy endpoint was achieved; the Arm A SVR_{12} rate (excluding prior SOF + RBV ± pegIFN failures) demonstrated noninferiority to the historical control rate for the standard-of-care (SOF + RBV for 12 weeks). Excluding prior SOF + RBV ± pegIFN failures in Arm A, the SVR_{12} rate of Arm A was also superior to the historical rate of 95% for the current standard-of-care, as the LCB of the 2-sided 95% CI was > 95%.

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

Assessment	Arm A (N = 196)
SVR_{12}, n/N (%)	195/196 (99.5)
95% CI	98.5, 100.0
Nonresponse, n/N (%)	1/196 (0.5)
Reason for nonresponse, n/N (%)	
Virologic failure	0/196
On-treatment virologic failure	0/196
$Relapse_{12}$	0/195
Nonvirologic failure	1/196 (0.5)
Premature study drug discontinuation	0/196
HCV reinfection	0/196
Missing SVR_{12} data	1/196 (0.5)
Other	0/196

Arm A: 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_{12} = 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 from a local laboratory present, then it was imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.

In Arm A, excluding prior SOF + RBV ± pegIFN failures, no subject experienced on-treatment virologic failure and no subject experienced $relapse_{12}$.

The percentage of subjects in Arm A who were prior SOF + RBV ± pegIFN failures and who achieved SVR_{12} was 100% (6 of 6 subjects). Both subjects in Arm B who were prior SOF + RBV ± pegIFN failures also achieved SVR_{12} after treatment with ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks in the OL Treatment Period.

Summary/Conclusions (Continued)

Resistance Results:

By phylogenetic analysis, 8 GT2 subtypes were detected within Arm A of the study (72 GT2a, 53 GT2b, 45 GT2c, 6 GT2i, 1 GT2k, 3 GT2l, 1 GT2q, and 1 GT2t), and subtype could not be determined on baseline samples from 8 GT2-infected subjects due to lack of homology with any known GT2 subtype. In addition, 4 subjects identified as having GT2 infection by the LiPA assay were determined to be infected with GT1b by phylogenetic analysis.

Baseline polymorphisms were not detected at any of the key subset of amino acid positions in NS3 (positions 155, 156, or 168) but were detected in 83.2% (149/179) of the GT2-infected subjects in NS5A (at positions 24, 28, 30, 31, 58, 92, or 93). The presence of baseline polymorphisms did not impact treatment outcome in subjects infected with any HCV subtype in this study, as no subject experienced virologic failure.

Pharmacokinetic Results:

Following administration of ABT-493/ABT-530 300 mg/120 mg QD, ABT-493 and ABT-530 plasma concentrations attained steady-state at 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 approximately 7 hours postdosing.

Safety Results:

During the DB Treatment Period, the percentage of subjects with AEs and with AEs considered related to direct-acting antiviral agents (DAAs) was comparable between treatment arms.

The majority of subjects experienced at least 1 AE during the DB Treatment Period, the most common overall being headache and fatigue. Most subjects who experienced AEs in the ABT-493/ABT-530 arm, Arm A, had events with a maximum severity of Grade 1 (mild) during the DB Treatment Period. Three subjects (1.5%) in Arm A and 1 subject (1.0%) in Arm B had serious AEs, none of which were considered by the investigator to be related to DAA treatment. No subject died or had an AE leading to premature discontinuation of study drug.

Few subjects had Grade 3/4 hematology or chemistry values that worsened compared with baseline during the DB Treatment Period. The majority of subjects with Grade 3/4 hematology or chemistry values had isolated values that were not clinically significant. No clinically meaningful observations were noted for urinalysis, vital signs, or 12-lead electrocardiogram assessments.

Conclusions:

- In HCV GT2-infected subjects (excluding prior SOF + RBV ± pegIFN failures) without cirrhosis who received the fixed-dose combination of ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks, high efficacy was achieved (SVR_{12} rate of 99.5%) The fixed-dose combination of ABT-493/ABT-530 for 12 weeks demonstrated noninferiority and superiority to the historical control rate for the standard-of-care (SOF + RBV for 12 weeks). There were no virologic failures among HCV GT2-infected subjects without cirrhosis who received ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks.
- Due to the lack of virologic failures, no negative predictors of response could be identified, including baseline HCV RNA, prior pegIFN/RBV or SOF/RBV ± pegIFN experience, or the presence of baseline at resistance-associated polymorphisms.

Summary/Conclusions (Continued)

Conclusions (Continued):

- 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 7 hours postdosing.
- The fixed-dose combination of ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks was well-tolerated, demonstrating a favorable safety profile, similar to the profile observed in subjects receiving placebo, with mostly mild AEs, rare, reversible occurrences of significant laboratory abnormalities, no premature discontinuations due to AEs, and no DAA-related serious AEs.