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, Open-Label, Active-Controlled, Multicenter Study to Compare Efficacy and Safety of ABT-493/ABT-530 to Sofosbuvir Co-Administered with Daclatasvir in Adults with Chronic Hepatitis C Virus Genotype 3 Infection (ENDURANCE-3)		
Coordinating Investigator: [redacted]		
Study Sites: 77 sites in Australia, Canada, France, Germany, New Zealand, Sweden, Switzerland, United Kingdom, and the United States		
Publications: 1 abstract		
Studied Period (Years): First Subject First Visit: 01 December 2015 Last Subject Last Visit for Primary Analysis: 24 October 2016	**Phase of Development:** 3	

Objectives:

The primary objectives of this study were to demonstrate noninferiority in the percentage of subjects achieving sustained virologic response 12 weeks postdosing (SVR_{12}) of 12 weeks of treatment with ABT-493/ABT-530 to 12 weeks of treatment with sofosbuvir (SOF) and daclatasvir (DCV), to demonstrate noninferiority of 8 weeks of treatment with ABT-493/ABT-530, and to assess safety of ABT-493/ABT-530 compared to SOF and DCV in adults with chronic hepatitis C virus (HCV) genotype 3 (GT3) infection.

The secondary objectives were to assess the superiority of 12 weeks of ABT-493/ABT-530 to SOF and DCV based on SVR_{12}, to assess the percentages of subjects with on-treatment virologic failure, and to assess the percentages of subjects with post-treatment relapse.

Additional objectives were to assess pharmacokinetics and emergence and persistence of viral variants in these treatment regimens.

Methodology:

This was a Phase 3, randomized, open-label, active-controlled multicenter study to compare efficacy and safety of ABT-493/ABT-530 to SOF and DCV in treatment-naïve chronic HCV GT3-infected subjects without cirrhosis.

HCV GT3-infected treatment-naïve subjects without cirrhosis were enrolled into 1 of 3 treatment arms:

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

Arm B: SOF 400 mg + DCV 60 mg QD for 12 weeks

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

Subjects meeting all eligibility criteria were initially randomized in a 2:1 ratio to Arms A or B. After enrollment in Arms A and B was completed, subjects were to be assigned to Arm C.

The planned total duration of the study (excluding screening) was up to 32 weeks for Arm C subjects and up to 36 weeks for Arms A and B subjects.

Number of Subjects (Planned and Analyzed):

Planned: 460 subjects (230 subjects in Arm A, 115 subjects in Arm B, 115 subjects in Arm C).

Analyzed: 506 subjects were randomized and 505 subjects (233 subjects in Arm A, 115 subjects in Arm B, and 157 subjects in Arm C) 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 GT3 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 (i.e., subject had never received any anti-HCV treatment).
- Documented as noncirrhotic.

Diagnosis and Main Criteria for Inclusion (Continued):

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 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.
- Consideration by the investigator, for any reason, that the subject was an unsuitable candidate to receive ABT-493/ABT-530, SOF, or DCV.
- History of severe, life-threatening, or other significant sensitivity to any excipients of the study drugs.
- Previous use of any anti-HCV treatment.

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, 15-006020, 16-001003

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 SOF 400 mg + DCV 60 mg QD for 12 weeks.

Subjects in Arm C received ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks.

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

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
Sofosbuvir	Gilead	Oral	Tablet	400 mg	15-003765 16-001070 15-004082
Daclatasvir	Bristol-Myers Squibb	Oral	Tablet	30 mg	15-005426[a] 15-005807[a]
				60 mg	15-005427 15-005811 15-005812

a. Daclatasvir 30 mg tablet bulk lots 15-005426 and 15-005807 were shipped to the sites, but no subjects took tablets from these lots.

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 and with available samples, the variants at signature amino acid positions (in nonstructural viral protein 3 [NS3] and nonstructural viral protein 5A [NS5A] for Arms A and C; in NS5A only for Arm B) 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 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 HCV viral resistance by NGS in Arms A and C.

Pharmacokinetics:

Plasma concentrations for ABT-493, ABT-530, SOF, GS-331007, and DCV were tabulated for each subject and group. Summary statistics were computed for each time and visit.

Safety:

Safety and tolerability were 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 achieving SVR_{12} (HCV RNA < lower limit of quantitation [LLOQ] 12 weeks after the last actual dose of study drug). The percentage of subjects achieving SVR_{12} in the intention-to-treat (ITT) population was calculated for each arm and 2-sided confidence intervals (CIs) for the within-arm SVR_{12} rates and for the differences in SVR_{12} rates (Arm A minus Arm B and Arm C minus Arm A) were calculated using the normal approximation to the binomial distribution.

Noninferiority in the SVR_{12} rate of the 12-week regimen (Arm A) to the standard of care (SOF + DCV) was demonstrated if the lower bound of the CI for the difference (Arm A minus Arm B) was above the noninferiority margin of –6% or if the lower bound of the CI for the SVR_{12} rate within Arm A was greater than 92%. Noninferiority of Arm C to Arm A was defined similarly. A Hochberg procedure was used to control for multiplicity within the first and second primary efficacy objectives.

To support the primary comparisons, the analyses were also conducted in per protocol populations.

Statistical Methods (Continued)

Efficacy (Continued):

Other secondary efficacy endpoints were:

- The percentage of subjects 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); and
- 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 subjects with reinfection [$Relapse_{12}$]).

Superiority of Arm A to Arm B would have been demonstrated if the lower bound of the CI for the difference in SVR_{12} rates between arms (Arm A minus Arm B) was above 0%.

The percentage of subjects with on-treatment virologic failure and post-treatment relapse was summarized for each treatment arm and for differences between arms, with 2-sided 95% CIs provided for rates within treatment arms and for the difference between arms. Wilson score intervals were used for within-arm summaries and for any between-arm summaries, unless otherwise specified. These endpoints were not part of the fixed-sequence testing procedure, as no hypothesis was being tested.

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_{12} 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_{12} and with $Relapse_{12}$ was presented for subgroup variables such as HCV GT3 subtype, interleukin 28B genotype, and baseline HCV RNA level.

Statistical Methods (Continued)

Pharmacokinetics:

Individual plasma concentrations of ABT-493, ABT-530, SOF, GS-331007, and DCV were tabulated for each subject and group. Results were tabulated for each subject and summary statistics were computed for each sampling time within each arm. Individual plasma concentrations of ABT-493, ABT-530, SOF, GS-331007, and DCV were summarized.

Safety:

All subjects who received at least 1 dose of study drug were included in the safety analyses. 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 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 were summarized descriptively by arm. The number and percentage of subjects with postbaseline values meeting toxicity grades and meeting potential hepatotoxicity criteria were summarized. Frequencies and percentages of subjects with postbaseline values meeting predefined criteria for potentially clinically significant vital sign values during treatment were summarized.

Efficacy Results:

In the ITT population, SVR_{12} was achieved by 95.3% (222/233) of subjects in Arm A, 96.5% (111/115) of subjects in Arm B, and 94.9% (149/157) of subjects in Arm C.

Summary/Conclusions

Efficacy Results (Continued):

Primary Efficacy Endpoint: SVR_{12} Within Treatment Arms (ITT Population)

	Arm A N = 233	Arm B N = 115	Arm C N = 157
SVR_{12}, n/N (%)	222/233 (95.3)	111/115 (96.5)	149/157 (94.9)
95% CI	92.6, 98.0	93.2, 99.9	91.5, 98.3
Nonresponse, n/N (%)	11/233 (4.7)	4/115 (3.5)	8/157 (5.1)
Reasons for nonresponse, n/N (%)			
Virologic failure	4/233 (1.7)	1/115 (0.9)	6/157 (3.8)
On-treatment virologic failure	1/233 (0.4)	0/115	1/157 (0.6)
Relapse	3/222 (1.4)	1/114 (0.9)	5/150 (3.3)
Nonvirologic failure	7/233 (3.0)	3/115 (2.6)	2/157 (1.3)
Premature study drug discontinuation	4/233 (1.7)	1/115 (0.9)	0/157
HCV reinfection	0/233	0/115	0/157
Missing SVR_{12} data	3/233 (1.3)	2/115 (1.7)	2/157 (1.3)
Other	0/233	0/115	0/157

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

Arm B: SOF 400 mg + DCV 60 mg QD for 12 weeks

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

CI = confidence interval; DCV = daclatasvir; HCV = hepatitis C virus; ITT = intention-to-treat; QD = once daily; RNA = ribonucleic acid; SOF = sofosbuvir; 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 to be imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.

In the comparison of Arms A and B, the lower bound of the 95% CI for the difference (Arm A minus Arm B) was –5.6%, which was above the noninferiority margin of –6%, and the lower bound of the 95% CI for the SVR_{12} rate within Arm A was greater than 92%. Therefore, based on the SVR_{12} rate, noninferiority of the 12-week ABT-493/ABT-530 regimen (Arm A) to the standard of care SOF + DCV 12-week regimen (Arm B) was achieved in the ITT population.

Summary/Conclusions (Continued)

Primary Efficacy Endpoint: SVR_{12} for Comparison of 12 Weeks of Treatment with ABT-493/ABT-530 Versus SOF + DCV (ITT and Per Protocol Populations)

	ITT Population		Per Protocol Population	
Assessment	**Arm A N = 233**	**Arm B N = 115**	**Arm A N = 230**	**Arm B N = 113**
SVR_{12}, n/N (%)	222/233 (95.3)	111/115 (96.5)	222/230 (96.5)	111/113 (98.2)
95% CI	92.6, 98.0	93.2, 99.9	94.2, 98.9	95.8, 100.0
Treatment difference (95% CI)	–1.2 (–5.6, 3.1)		–1.7 (–5.1, 1.7)	
Threshold for within Arm A	92%		92%	
Non-inferiority margin	–6%		–6%	

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

Arm B: SOF 400 mg + DCV 60 mg QD for 12 weeks

CI = confidence interval; DCV = daclatasvir; HCV = hepatitis C virus; ITT = intention-to-treat; QD = once daily; RNA = ribonucleic acid; SOF = sofosbuvir; 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 to be imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.

In the comparison of Arms C and A, the lower bound of the 97.5% CI for the difference (Arm C minus Arm A) was –5.4%, which was above the noninferiority margin of –6%. Therefore, noninferiority of the 8-week ABT-493/ABT-530 regimen (Arm C) to that of the 12-week ABT-493/ABT-530 (Arm A) was achieved in the ITT population.

Summary/Conclusions (Continued)

Primary Efficacy Endpoint: SVR_{12} for Comparison of 8 Weeks and 12 Weeks of Treatment with ABT-493/ABT-530 (ITT and Per Protocol Populations)

	ITT Population		Per Protocol Population	
Assessment	**Arm C N = 157**	**Arm A N = 233**	**Arm C N = 152**	**Arm A N = 225**
SVR_{12}, n/N (%)	149/157 (94.9)	222/233 (95.3)	146/152 (96.1)	221/225 (98.2)
95% CI	91.5, 98.3	92.6, 98.0	93.0, 99.1	96.5, 99.9
Treatment difference (97.5% CI)	–0.4 (–5.4, 4.6)		–2.2 (–6.2, 1.9)	
Treatment difference (95% CI)	–0.4 (–4.8, 4.0)		–2.2 (–5.7, 1.4)	
Threshold for within Arm C	92%		92%	
Non-inferiority margin	–6%		–6%	

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

Arm C: ABT-493/ABT-530 300 mg/120 mg QD for 8 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 to be imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.

Resistance Results:

The prevalence of baseline polymorphisms in NS3 at a key subset of amino acid positions 155, 156, or 168 was 1.8% (4/228) and 1.3% (2/155) in Arm A and Arm C, respectively. The prevalence of baseline polymorphisms in NS5A at a key subset of amino acid positions 24, 28, 30, 31, 58, 92, or 93 was 19.2% (44/229) and 27.7% (43/155) in Arm A and Arm C, respectively. Baseline polymorphisms across both NS3 and NS5A were detected in 1.3% (3/228) and 1.3% (2/155) of the subjects in Arm A and Arm C, respectively.

Among subjects in this study, baseline polymorphisms in NS3 and most polymorphisms in NS5A including Y93H did not have an apparent impact on treatment outcome. A30K in NS5A appeared to be associated with a somewhat reduced SVR_{12} rate.

Pharmacokinetic Results:

Pharmacokinetic exposures of ABT-493 and ABT-530 in HCV GT3-infected treatment-naïve subjects without cirrhosis were summarized. ABT-493 and ABT-530 concentrations quickly increased postdose to the maximum level at approximately 4 hours and 7 hours, respectively. There was minimal drug accumulation for both ABT-493 and ABT-530 during the Treatment Period. The pharmacokinetics of SOF, GS-331007, and DCV observed in this study were also summarized.

Summary/Conclusions (Continued)

Safety Results:

The percentage of subjects with AEs and with AEs considered related to study drug was comparable among treatment arms. The majority of subjects experienced at least 1 AE. Most subjects with AEs experienced AEs with a maximum severity of Grade 1 (mild), with the most common (≥ 10.0% of subjects) overall being headache, fatigue, and nausea. Two subjects (1 in Arm A, 1 in Arm B) experienced AEs ≥ Grade 3 in severity (migraine and irritability, respectively) that were considered related to study drug. No subject experienced a serious AE (SAE) related to study drug. Two subjects died during the post-treatment follow-up period due to nontreatment-emergent SAEs of death (Arm B) and accidental overdose (Arm C), both of which were considered not related to study drug and involved overdoses with recreational drugs. Four subjects (3 in Arm A and 1 in Arm B) had an AE leading to premature discontinuation of study drug; in 2 subjects (1 each in Arms A and B), the AEs were considered related to the study drugs.

Few subjects had Grade 3/4 hematology or chemistry values that worsened compared with baseline during the Treatment Period. The majority of subjects with Grade 3/4 hematology or chemistry values had values that were isolated events and not clinically significant. There were no subjects with clinically meaningful alanine aminotransferase and/or bilirubin elevations. No cases of drug-induced liver injury or hepatic decompensation were identified. No clinically meaningful observations were noted for urinalysis, vital signs, or 12-lead electrocardiogram assessments.

Conclusions:

In HCV GT3 treatment-naïve subjects without cirrhosis, results of this study demonstrated the following:

- The SVR_{12} rate in the 12-week ABT-493/ABT-530 300/120 mg QD arm was noninferior to that in the SOF + DCV arm.
- The SVR_{12} rate in the 8-week ABT-493/ABT-530 300/120 mg QD arm was noninferior to that in the 12-week ABT-493/ABT-530 300/120 mg QD.
- Rates of virologic failure were low across the study arms.
- Pharmacokinetic exposures of ABT-493 and ABT-530 in HCV GT3-infected treatment-naïve subjects without cirrhosis were summarized. ABT-493 and ABT-530 concentrations quickly increased postdose to the maximum level at approximately 4 hours and 7 hours, respectively. There was minimal drug accumulation for both ABT-493 and ABT-530 during the Treatment Period. The pharmacokinetics of SOF, GS-331007, and DCV observed in this study were also summarized.
- ABT-493/ABT-530 300/120 mg QD demonstrated a favorable safety profile and was well tolerated. The safety and tolerability of the ABT-493/ABT-530 regimens were comparable to those of the SOF + DCV regimen.