2.0 Synopsis

AbbVie GK	**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*, 24*aR*)-7-*tert*-butyl-*N*-[(1*R*,2*R*)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl)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 ABT-530: Methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate		
Title of Study: A Randomized, Open-Label, Active Comparator, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Japanese Adults with Genotype 2 Chronic Hepatitis C Virus Infection (CERTAIN-2)		
Coordinating Investigator: [redacted]		
Study Sites: A total of 56 investigative sites were approved to receive drug supplies on behalf of AbbVie and screen and enroll subjects into the study.		
Publications: Not applicable		

Studied Period (Years): First Subject First Visit: 08 April 2016 Last Subject Last Visit: 24 March 2017	**Phase of Development:** 3

Objectives:

The primary objectives of this study were to assess:

- The efficacy (sustained virologic response 12 weeks post dosing [SVR_{12}]) and safety of 8 weeks of treatment with the combination regimen ABT-493/ABT-530 compared to 12 weeks of treatment with sofosbuvir (SOF) plus ribavirin (RBV) in hepatitis C virus (HCV) genotype (GT)2-infected direct-acting antiviral agent (DAA) treatment-naïve Japanese adults without cirrhosis

The secondary objectives were to assess:

- The percentage of subjects achieving SVR_{12} in HCV GT2-infected Japanese adults without cirrhosis treated with the ABT-493/ABT-530 combination regimen;
- The percentages of subjects with on-treatment virologic failure;
- The percentages of subjects with post-treatment relapse.

Additional objectives were to assess pharmacokinetic (PK) and emergence and persistence of viral variants in these treatment regimens.

Methodology:

This is a Phase 3, multicenter study to evaluate efficacy, safety, and PK of coformulated ABT-493/ABT-530 (300 mg/120 mg) once daily (QD) in chronic HCV-infected, HCV DAA treatment-naïve Japanese adult subjects. This study is randomized, open-label, and active-controlled, wherein HCV DAA treatment-naïve, GT2-infected subjects without cirrhosis were enrolled.

HCV GT2-infected DAA treatment-naïve subjects (including subjects who are interferon [IFN] treatment experienced with or without RBV) without cirrhosis were enrolled into 1 of 2 treatment arms (80 subjects into Arm A and 40 subjects into Arm B):

- Arm A: ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks;
- Arm B: SOF 400 mg QD plus RBV (600 – 1000 mg based on weight divided twice daily [BID]) for 12 weeks.

Randomization was stratified by prior IFN-experience (naïve versus experienced), and Screening HCV ribonucleic acid (RNA) viral load (< or ≥ 6 million International Units [IU]/mL).

This study consisted of a treatment period and post-treatment period, as described below:

Treatment Period: Subjects enrolled received 8 weeks of ABT-493/ABT-530 or 12 weeks of SOF plus RBV.

Post-Treatment Period: Subjects who completed the Treatment Period, experienced on-treatment virologic failure, or prematurely discontinued the Treatment Period were followed for 24 weeks after receipt of the last dose of study drug to monitor safety, HCV RNA levels, and to evaluate efficacy and the emergence and persistence of viral resistance-associated variants.

Number of Subjects (Planned and Analyzed):

The study was designed to enroll 120 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations (80 subjects in the ABT-493/ABT-530 8-week arm [Arm A] and 40 subjects in the SOF + RBV 12-week arm [Arm B]). A total of 136 subjects were enrolled (90 in Arm A and 46 in Arm B) in the study at 56 study sites.

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria:

- Subjects were Japanese males or females at least 18 years of age.
- Females were postmenopausal for at least 2 years; surgically sterile or had a vasectomized partner; or, if of childbearing potential and sexually active with a male partner, were currently using at least 1 effective method of birth control at the time of Screening and agreed to practice 1 effective method of birth control for subjects randomized to Arm A and 2 effective methods of birth control for subjects randomized to Arm B from Screening through 30 days after stopping study drug in Arm A and 6 months after stopping study drug for Arm B. Sexually active males were surgically sterile or, if sexually active with a female partner of childbearing potential, agreed to practice 1 effective form of birth control from Screening through 30 days after stopping study drug in Arm A and 6 months after stopping study drug for Arm B.
- All subjects had chronic HCV infection with a single GT2; positive results for anti-HCV antibody; and a plasma HCV RNA viral load of ≥ 1000 IU/mL at Screening.
- Subjects were defined as HCV DAA treatment-naïve if they had not received a single dose of any approved or investigational DAA. All previous HCV IFN treatment must have been completed at least 2 months prior to Screening.
- All subjects were documented as non-cirrhotic.

Main Exclusion Criteria:

- Females who were pregnant or planned to become pregnant, or breastfeeding or males whose partner was pregnant or planning to become pregnant during the study.
- Subjects coinfected with hepatitis B virus or human immunodeficiency virus.
- Use of contraindicated medications or supplements within 2 weeks or 10 half-lives (if known), whichever was longer, prior to the first dose of any study drug.
- Any cause of liver disease other than chronic HCV infection.
- Any current or past clinical evidence of Child-Pugh B or C classification or clinical history of decompensated liver disease (e.g., ascites noted on physical exam, hepatic encephalopathy, or variceal bleeding).
- Any of the following laboratory abnormalities:
  - Creatinine clearance (CrCl) ≤ 50 mL/min
  - Albumin < lower limit of normal
  - International normalized ratio (INR) ≥ 1.2 (subjects with a known inherited blood disorder and INR ≥ 1.2 could be enrolled with permission of the AbbVie designated physician.)
  - Hemoglobin < 12 g/dL
  - Platelets < 90,000 cells/mm^3

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	15-006595

Duration of Treatment:

Subjects received ABT-493/ABT-530 (300/120 mg) for 8 weeks or SOF (400 mg QD) + RBV (600 – 1000 mg based on weight divided BID) 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 Numbers
SOF	Gilead	Oral	Tablet	400 mg	AA0051
RBV	MSD	Oral	Capsules	200 mg	A003M, B001B

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.

The primary efficacy variable was SVR_{12} (HCV RNA < lower limit of quantification 12 weeks after the last actual dose of study drug).

The secondary efficacy variables were on-treatment virologic failure and post-treatment relapse.

Resistance:

For all subjects receiving ABT-493/ABT-530, the variants at signature resistance-associated amino acid positions at baseline identified by population or deep sequencing and relative to the appropriate prototypic reference sequence were analyzed.

The following resistance information was analyzed for subjects receiving ABT-493/ABT-530 who did not achieve SVR_{12} and who had a post-baseline sample with HCV RNA ≥ 1000 IU/mL:

- The amino acid variants in available post-baseline samples identified by population or deep sequencing and comparison to the baseline sequence
- 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
- The persistence of viral resistance by population or deep sequencing.

Safety:

Safety and tolerability was assessed by monitoring adverse events (AEs), which include common AEs, serious AEs (SAEs), AEs that cause treatment discontinuation and deaths, changes in vital signs, physical examination findings, 12-lead electrocardiograms, and laboratory tests assessments.

Pharmacokinetics:

Individual plasma concentrations of ABT-493, ABT-530, SOF, GS-331007 (SOF metabolite), and RBV were tabulated and summarized.

Pharmacogenetics:

Interleukin 28B status was determined for each subject and analyzed as a factor contributing to the subject's response to study treatment.

Criteria for Evaluation (Continued):

Quality of Life:

The following patient-reported outcomes (PROs) were evaluated: EuroQol 5 Dimensions 3 Levels Health State Instrument (EQ-5D-3L health index), EuroQol 5 Dimensions 3 Levels visual analogue scale (EQ-5D-3L VAS), and Fatigue Severity Scale (FSS).

Statistical Methods

All analyses were performed on randomized subjects who received at least 1 dose of study drug, unless otherwise specified. No data were imputed for any efficacy or safety analysis except for analyses of sustained virologic response (SVR) endpoints (HCV RNA data) and the PRO questionnaires.

Efficacy:

Primary Efficacy Endpoint

The primary efficacy endpoint was to show noninferiority in SVR_{12} rates of the 8-week regimen (Arm A) compared with the 12-week regimen (Arm B), the percentage of subjects achieving SVR_{12} was calculated for each arm on the intention-to-treat (ITT) population. A 2-sided 95% confidence interval (CI) for the difference in SVR_{12} rates (Arm A minus Arm B) was calculated.

Secondary Endpoints

The percentage of subjects in Arm A achieving SVR_{12} in the ITT population, the percentage of subjects with on-treatment virologic failure, and the percentage of subjects with post-treatment relapse was summarized along with 95% CIs, where applicable, using the normal approximation to the binomial distribution or the Wilson score methods.

Patient-Reported Outcomes

The mean change from baseline to each applicable post-baseline time point in the FSS total score, EQ-5D-3L health index score, and EQ-5D-3L VAS score was summarized descriptively at each visit and for change from baseline to each visit by treatment arm. For each of these scores, mean change from Baseline to the Final Treatment Visit and from Baseline to Post-Treatment Week 12 was compared between treatment arms using an analysis of covariance model with treatment arm as a factor and baseline score as a covariate.

Resistance:

The following resistance information was analyzed for all baseline samples from subjects in Arm A: 1) the prevalence of polymorphisms at signature amino acid positions at baseline identified by next-generation sequencing (NGS) was compared to the appropriate subtype specific prototypic reference sequence; and, (2) a comparison of SVR_{12} rates in subjects with or without baseline variants was conducted. For subjects not achieving SVR_{12} or SVR_{24}, treatment-emergent substitutions at postbaseline time points were identified by NGS relative to the respective baseline sequence and to a subtype-specific reference sequence.

HCV Genotype/Subtype:

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

Statistical Methods (Continued)

Safety:

The number and percentage of subjects in each arm with treatment-emergent AEs (TEAEs; defined as any event that began or worsened in severity after initiation of study drug through 30 days post-study drug dosing) were tabulated by primary Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and preferred term and compared between arms using Fisher's exact test. The number of subjects with TEAEs by severity grade and relationship to study drug was also tabulated. Subjects reporting more than 1 AE for a given MedDRA preferred term or SOC were counted only once for that term or SOC using the most severe grade for the severity grade table and the most related for the relationship to study drug tables.

Clinical laboratory test values and changes from baseline were summarized by arm at each visit. Mean changes from baseline to each post-baseline visit were compared between arms using contrasts within an analysis of variance (ANOVA) model with treatment arm as the factor. The number and percentage of subjects with post-baseline shifts or a maximum of at least Grade 3 for all laboratory parameters were summarized by arm. Laboratory abnormalities (by toxicity grade) for each parameter were compared using Fisher's exact tests.

Mean changes in vital signs from baseline to each post-baseline visit were summarized descriptively by arm and compared using contrasts within an ANOVA model with treatment arm as the factor. Frequencies and percentages of subjects with post-baseline values meeting pre-defined criteria for potentially clinically significant vital signs values were summarized and compared using Fisher's exact tests.

Pharmacokinetic:

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

Summary/Conclusions

Efficacy Results:

HCV GT2-infected DAA-treatment naïve, non-cirrhotic Japanese subjects treated with ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks achieved a high SVR_{12} rate of 97.8% (95% CI: 92.3% to 99.4%) versus 93.5% (95% CI: 82.5% to 97.8%) for subjects treated with SOF 400 mg QD + RBV 600 – 1000 mg based on weight divided BID for 12 weeks. The 8-week regimen of ABT-493/ABT-530 (SVR_{12} rate: 97.8%) was noninferior to 12 weeks of SOF + RBV (SVR_{12} rate: 93.5%), as the difference between arms was 4.3% with 95% CI (–3.5% to 12.1%; lower confidence bound above the noninferiority margin –10%). Subjects in Arm A who received ABT-493/ABT-530 achieved high efficacy across relevant subgroups and none experienced on-treatment virologic failure or post-treatment relapse through post-treatment Week 24.

Summary/Conclusions (Continued)

Resistance Results:

Based on phylogenetic analysis, the following subtypes were identified in Arm A of the study: GT2a 72.2% (65/90) and GT2b 27.8% (25/90).

The prevalence of baseline polymorphisms at signature amino acid positions in nonstructural viral protein 3 (NS3) at 15% detection threshold was 9.2% (6/65) and 4.0% (1/25) in GT2a- and GT2b-infected subjects in Arm A, respectively. The prevalence of baseline polymorphisms at signature amino acid positions in nonstructural viral protein 5A (NS5A) was high (96.9% [63/65] in GT2a- and 32.0% [8/25] in GT2b-infected subjects in Arm A), and the L/M31 polymorphism was the most frequent. Baseline polymorphisms in NS3 and/or NS5A had no impact on treatment outcome as no subject in Arm A experienced virologic failure.

Two GT2a-infected subjects in Arm B experienced virologic failure. Neither subject had baseline polymorphisms or treatment-emergent substitutions at signature amino acid positions in nonstructural viral protein 5B (NS5B).

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 Week 1 Visit. ABT-493 and ABT-530 concentrations remained constant throughout the Treatment Period (Week 1 to Week 8) and no apparent drug accumulation was observed.

Safety Results:

- The fixed dose combination of ABT-493/ABT-530 300 mg/120 mg QD administered for 8 weeks was well tolerated by Japanese subjects with HCV GT2 infection without cirrhosis.
- Subjects treated with ABT-493/ABT-530 treatment had fewer overall TEAEs and TEAEs related to treatment compared to SOF + RBV treatment. Subjects treated with SOF + RBV had higher rates of anemia, hyperbilirubinemia, and hyperuricemia.
- Overall among subjects treated with ABT-493/ABT-530, the most common (≥ 5% of subjects) TEAEs were nasopharyngitis, headache, and malaise. No TEAE related to treatment was reported in > 5% of subjects treated with ABT-493/ABT-530. The most common (≥ 5% of subjects) TEAEs reported among subjects receiving SOF + RBV were anemia, blood bilirubin increased, malaise, nasopharyngitis, nausea, stomatitis, and hyperuricemia. TEAEs related to SOF + RBV reported in > 5% of subjects included anemia and blood bilirubin increased. The higher rates of these events related to SOF + RBV are likely due to the effect of RBV.
- The majority of patients who experienced TEAEs had a maximum severity of Grade 1 (mild).
- Serious TEAEs were infrequent in both arms and only 1 (Castleman's disease in a subject who received SOF + RBV) was related to treatment. Discontinuations due to AEs were also infrequent. No deaths were reported.
- No clinically significant laboratory abnormalities or trends were observed with ABT-493/ABT-530, while SOF + RBV treatment led to clinically relevant declines in hemoglobin and increases in total bilirubin.
- There were no treatment-emergent alanine aminotransferase elevations greater than baseline in either the ABT-493/ABT-530 or SOF + RBV arms, and no cases of drug-induced liver injury or hepatic decompensation were identified.

Summary/Conclusions (Continued)

Conclusions:

- Based on SVR_{12} results, the fixed dose regimen of ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks achieved high efficacy (SVR_{12} rate of 97.8%) without virologic failures in non-cirrhotic, DAA-naïve, Japanese subjects with HCV GT2 infection. High SVR_{12} rates were achieved across all subgroups based on demographics or baseline characteristics. No subject who achieved SVR_{12} relapsed after Post Treatment Week 12.
- The 8-week regimen of ABT-493/ABT-530 (SVR_{12} rate: 97.8%) was noninferior to 12 weeks of SOF + RBV (SVR_{12} rate: 93.5%), as the difference between arms was 4.3% with 95% CI (–3.5% to 12.1%; lower confidence bound above the noninferiority margin –10%).
- ABT-493 and ABT-530 plasma concentrations attained steady state by Week 1 Visit and remained constant throughout the Treatment Period (Week 1 to Week 8). No apparent drug accumulation was observed.
- The ABT-493/ABT-530 regimen was safe and well tolerated with AEs that were mostly Grade 1 (mild) in severity and few serious TEAEs or TEAEs leading to discontinuation. The most common TEAEs reported with ABT-493/ABT-530 treated subjects were nasopharyngitis, headache, and malaise. No ABT-493/ABT-530-related TEAEs occurred in ≥ 5% of subjects.
- No unique safety concerns were identified in subjects who received ABT-493/ABT-530. No subject experienced an event of hepatic decompensation, and there were no suspected cases of drug-induced liver injury.