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 Single-Arm, Open-Label, Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Renally-Impaired Adults with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (EXPEDITION-4)		
Coordinating Investigator: [redacted]		
Study Sites: 30 sites in Australia, Belgium, Canada, France, Greece, Italy, New Zealand, United Kingdom, and the United States		
Publications: None		
Studied Period (Years): First Subject First Visit: 21 December 2015 Last Subject Last Visit for Primary Analysis: 28 September 2016	**Phase of Development:** 3	

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_{12}) after 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) 1 – GT6 infection with chronic renal impairment.

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

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

Methodology:

This was a Phase 3, single arm, open-label, multicenter study to evaluate the efficacy and safety of ABT-493/ABT-530 for 12 weeks in HCV GT1 – GT6 infected treatment-naïve or prior treatment-experienced (i.e., had failed prior interferon [IFN] or pegylated interferon [pegIFN] with or without ribavirin [RBV], pegIFN/RBV plus sofosbuvir [SOF], or SOF plus RBV) subjects with or without cirrhosis, who had severe renal impairment or end-stage renal disease, including those on dialysis.

Subjects were categorized during screening as having chronic kidney disease (CKD) Stage 4 or Stage 5. Among HCV GT3-infected subjects, only treatment-naïve subjects with or without cirrhosis were eligible for enrollment.

Safety and efficacy were assessed by AbbVie 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 100 subjects.

Analyzed: 104 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 approved contraceptive methods) at least 18 years of age at time of screening.
- Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 as estimated by the Modification of Diet in Renal Disease method at screening according to the following formula: eGFR (mL/min/1.73 m^2) = 175 × (serum creatinine)$^{-1.154}$ × age$^{-0.203}$ × (0.742 if female) × (1.212 if black), or were dialysis-dependent. Subjects requiring dialysis must have been receiving dialysis or for at least 1 month prior to enrollment.
- Screening laboratory result indicating HCV GT1, 2, 3, 4, 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.

Diagnosis and Main Criteria for Inclusion (Continued):

Main Inclusion Criteria (Continued):

- Hepatitis C virus treatment-naïve (i.e., had not received a single dose of any approved or investigational regimen for the treatment of HCV) or received prior HCV treatment with IFN or pegIFN with or without RBV, pegIFN/RBV plus SOF, or SOF plus RBV.
- Documented as cirrhotic or noncirrhotic at any time previous to or at screening.

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.
- Hepatitis C virus GT3-infected, treatment-experienced subjects.
- Patients who failed a previous regimen containing protease inhibitors and/or nonstructural viral protein 5A inhibitors.
- Any cause of liver disease other than chronic HCV infection.
- History of solid organ transplantation, unless the implanted organ had since been removed, or was nonfunctional, and subject was no longer on immunosuppressive medication. If the organ was nonfunctional, the subject must have been clinically stable off of immunosuppressive medication for a minimum of 6 months prior to screening.
- Clinical history of acute renal failure in the 3 months prior to screening.
- Planned renal transplant during the course of the study (treatment and post-treatment).
- 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	15-006020, 15-006595

Duration of Treatment:

Subjects received ABT-493/ABT-530 300 mg/120 mg once daily (QD) for 12 weeks.

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.

Criteria for Evaluation (Continued)

Resistance:

For all subjects, the variants in available samples at signature resistance-associated 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 to be analyzed for subjects receiving active study drug who did not achieve SVR_{12} 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 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 and summarized.

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 who achieved SVR_{12} (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_{12} were summarized with a 2-sided 95% confidence interval (CI), calculated using the normal approximation to the binomial distribution. If the SVR_{12} 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 failures (defined as confirmed increase of > 1 $\log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA $\geq$ 100 IU/mL after HCV RNA < LLOQ during treatment, or HCV RNA $\geq$ LLOQ at the 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 the 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 the analysis of relapse, a subject was considered to have completed treatment if they had a study drug duration of 77 days or greater. Subjects considered to have reinfection were excluded from the relapse summary. 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.

Statistical Methods (Continued)

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 calculated, along with the corresponding 2-sided 95% Wilson score intervals, for subgroup variables such as CKD stage, presence or absence of cirrhosis, HCV genotype 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 at visits with intensive pharmacokinetic sample collections (Week 4 and Week 4 + 1 Day visits). Results were tabulated for each subject and summary statistics were computed for each sampling time. Individual plasma concentrations of ABT-493 and ABT-530 for visits after Week 1 were summarized by binned concentrations.

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 primary Medical Dictionary for Regulatory Activities (MedDRA®) 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 toxicity grades and 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 vital sign values were summarized.

Summary/Conclusions

Efficacy Results:

SVR_{12} was achieved by 98.1% (102/104) of subjects treated with ABT-493/ABT-530 (ITT population), with 2-sided 95% CI of 95.4% to 100.0%. No subject experienced on-treatment virologic failure or post-treatment relapse. High efficacy was observed regardless of baseline host or viral factors, including demographics, baseline HCV RNA levels, HCV genotype, CKD stage, cirrhosis status, relevant comorbidities, and prior treatment history.

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

Assessment	ABT-493/ABT-530 (N = 104)
SVR_{12}, n/N (%)	102/104 (98.1)
95% CI	95.4, 100.0
Nonresponse, n/N (%)	2/104 (1.9)
Reason for nonresponse, n/N (%)	
Virologic failure	0/104
On-treatment virologic failure	0/104
Relapse	0/100
Non-virologic failure	2/104 (1.9)
Premature study drug discontinuation	1/104 (1.0)
HCV reinfection	0/104
Missing SVR_{12} data	1/104 (1.0)
Other	0/104

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 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 98 subjects, 2 GT1, 5 GT2, 1 GT3, 9 GT4, 1 GT5, and 1 GT6 subtypes were identified in the study, including 24 GT1a, 28 GT1b, 4 GT2a, 4 GT2b, 2 GT2c, 1 each GT2i and GT2q, 11 GT3a, 5 GT4a, 2 GT4d, 3 GT4k, 4 GT4r, 1 each GT4c, 4g, 4n, 4o, 4t, 1 GT5a, and 1 GT6e-infected subjects. In addition, the subtype for 2 GT2-infected subjects could not be determined by phylogenetic analysis.

Summary/Conclusions (Continued)

Resistance Results (Continued):

Baseline polymorphisms at the key subset of amino acid positions in NS3 (positions 155, 156, or 168) were not detected in GT2-, GT3-, GT5-, or GT6-infected subjects, and were detected in 2.0% (1/51) and 5.3% (1/19) of the GT1- and GT4-infected subjects, respectively. NS5A polymorphisms (at positions 24, 28, 30, 31, 58, 92, or 93) were not detected in the GT5-infected subject, and were detected in 11.8% (6/51), 100% (12/12), 18.2% (2/11), 31.3% (5/16), and 100% (1/1), of the GT1-, GT2-, GT3-, GT4-, 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 none of the subjects experienced virologic failure.

Pharmacokinetic Results:

ABT-493 and ABT-530 do not appear to be extracted during hemodialysis. These data support that no dose adjustment is necessary for the direct-acting antiviral agents when administered to HCV-infected subjects with CKD, including those on dialysis.

Safety Results:

The majority of subjects experienced at least 1 AE during the Treatment Period. Most subjects experienced AEs with a maximum severity of Grade 1 (mild) or Grade 2 (moderate). One subject died during the follow-up period due to a serious AE of cerebral hemorrhage, an event considered not related to study drug. Twenty-five subjects experienced serious AEs, none of which was considered related to study drug. Four subjects had an AE leading to premature discontinuation of study drug (1 subject due to AEs of hypertension and hypertensive crisis, 1 subject due to AEs of cardiac failure congestive, hypertensive cardiomyopathy, hypertensive crisis, and pulmonary edema, 1 subject due to diarrhea, and 1 subject due to pruritus); of these, the AEs of diarrhea and pruritus were considered related to study drug while all other AEs were considered not related to study drug.

Few subjects had Grade 3/4 hematology or chemistry values that worsened compared with baseline during the Treatment Period. All Grade 3/4 values were considered not clinically significant because they were isolated or were not unexpected due to the subject's medical history and/or the fact that the subject was receiving hemodialysis. There were no events of hepatic decompensation or suspected events of drug-induced liver injury.

No clinically meaningful observations were noted for vital signs or 12-lead electrocardiogram assessments.

Conclusions:

- In subjects with CKD Stage 4 and CKD Stage 5, including subjects receiving dialysis, the fixed-dose combination of ABT-493/ABT-530 300 mg/120 mg QD given for 12 weeks demonstrated high efficacy; the SVR_{12} rate was 98.1%.
- No subjects experienced virologic failure.
- High efficacy was observed regardless of baseline host or viral factors, including demographics, baseline HCV RNA levels, HCV genotype, CKD stage, cirrhosis status, relevant comorbidities, prior treatment history, or presence of preexisting baseline polymorphisms.
- The favorable efficacy, safety, and pharmacokinetic profile for ABT-493/ABT-530 support the use of this regimen in subjects with severe renal impairment or on dialysis without the need for dose modification.