2.0 Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
ABT-493/ABT-530</td></tr>
<tr><td>Name of Active Ingredient:
ABT-493: (3aR,7S,10S,12R,21E,24aR)-7-tert-butyl-N-{(1R,2R)-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-1H,10H-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</td></tr>
<tr><td colspan="3">Title of Study: A Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 1, 2, 4, 5 or 6 Infection and Compensated Cirrhosis (EXPEDITION-1)</td></tr>
<tr><td colspan="3">Coordinating Investigator: [redacted]</td></tr>
<tr><td colspan="3">Study Sites: 40 sites in Belgium, Canada, Germany, South Africa, Spain, and the United States.</td></tr>
<tr><td colspan="3">Publications: none</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 07 December 2015
Last Subject Last Visit for Primary Analysis: 27 October 2016</td><td>Phase of Development: 3</td></tr>
</table>

Objectives:

The primary objectives of this study were to evaluate the effect of response to treatment by evaluating the percentage of subjects achieving sustained virologic response 12 weeks postdosing (SVR_{12}) following 12 weeks of treatment with ABT-493/ABT-530 and to evaluate the safety of ABT-493/ABT-530 in adults with chronic hepatitis C virus (HCV) genotype (GT) 1, 2, 4, 5, or 6 infection and compensated cirrhosis.

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

Additional objectives were to assess pharmacokinetics and the emergence and persistence of viral variants in 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 in chronic HCV GT1-, 2-, 4-, 5-, or 6-infected subjects with cirrhosis who were either HCV treatment-naïve or prior treatment-experienced (i.e., interferon [IFN] or pegylated interferon [pegIFN] ± ribavirin [RBV] or sofosbuvir [SOF] + RBV ± pegIFN).

Safety and efficacy were assessed throughout the study.

In the Post-Treatment Period, all subjects administered at least 1 dose of study drug were to be 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 175 subjects.

Analyzed: 146 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) subjects at least 18 years of age at time of screening.
- Screening laboratory result indicating HCV GT1, 2, 4, 5, or 6 infection.
- Compensated cirrhosis, defined as Child-Pugh score ≤ 6 at screening and no current or past clinical evidence of Child-Pugh B or C classification or clinical history of liver decompensation, including ascites noted on physical examination, bleeding varices, use of beta-blockers or diuretics for portal hypertension or ascites, or hepatic encephalopathy, and with documented cirrhosis.
- 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 ± RBV or SOF + RBV ± pegIFN therapy. Previous HCV treatment with any other approved or investigational medications was not allowed.

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.
- Screening laboratory analyses showing any of the following abnormal laboratory results:
  - Alanine aminotransferase > 10 × upper limit of normal (ULN)
  - Aspartate aminotransferase > 10 × ULN
  - Calculated creatinine clearance (using Cockcroft-Gault method) of < 50 mL/min
  - Total bilirubin ≥ 3.0 mg/dL
  - Albumin < 2.8 g/dL
  - International normalized ratio (INR) > 2.3, unless subject has known hemophilia or is on a stable anticoagulant regimen affecting INR
  - Hemoglobin < 11 g/dL for women; < 12 g/dL for men
  - Platelets < 60,000 cells per mm^3
- History of solid organ transplantation.
- 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

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 ABT-493/ABT-530, the variants in available samples at signature resistance-associated amino acid positions at baseline identified by population or deep sequencing and comparison to the appropriate prototypic reference sequence were analyzed.

The following resistance information was to be analyzed for subjects receiving ABT-493/ABT-530 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 population, deep, or clonal nucleotide sequencing, and comparison to the baseline sequence, 2) the amino acid variants in available postbaseline samples at signature resistance-associated positions identified by population or deep sequencing and comparison to the appropriate prototypic reference sequence, and 3) the persistence of viral resistance by population, deep, or clonal nucleotide sequencing.

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 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%, 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 $\log_{10}$ 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);
- 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; with further breakdown by relapse versus reinfection based on HCV population sequencing).

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. The percentage of subjects with on-treatment virologic failure and post-treatment relapse 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 (NS3/4A) 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 subtype.

Subgroup:

The percentage of subjects 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 genotype and available 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 (Day 1 and Week 4). 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.

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® 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 99.3% (145/146) of subjects treated with ABT-493/ABT-530 (ITT population), with 2-sided 95% CI of 98.0% to 100.0%. No subject demonstrated on-treatment virologic failure. One subject experienced post-treatment relapse (1/144). High efficacy was observed across HCV genotypes, regardless of demographics and baseline characteristics, including baseline HCV RNA levels, relevant comorbidities, or prior treatment history.

Summary/Conclusions (Continued)

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

Assessment	ABT-493/ABT-530 (N = 146)
SVR_{12}, n/N (%)	145/146 (99.3)
95% CI	98.0, 100.0
Nonresponse, n/N (%)	1/146 (0.7)
Reason for nonresponse, n/N (%)	
Virologic failure	1/146 (0.7)
On-treatment virologic failure	0/146
Breakthrough	0/146
End-of-treatment failure	0/146
Relapse	1/144 (0.7)
Non-virologic failure	0/146
Premature study drug discontinuation	0/146
HCV reinfection	0/146
Missing SVR_{12} data	0/146
Other	0/146

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 142 subjects, 3 GT1, 3 GT2, 5 GT4, 1 GT5, and 3 GT6 subtypes were identified in the study, including 50 GT1a-, 39 GT1b-, 1 GT1g-, 2 GT2a-, 24 GT2b-, 2 GT2c-, 7 GT4a-, 4 GT4d-, 1 GT4k-, 1 GT4o-, 2 GT4q-, 2 GT5a-, 1 GT6a-, 5 GT6e-, and 1 GT6t-infected subjects.

Baseline polymorphisms at the key subset of amino acid positions in NS3 (positions 155, 156, or 168) were not detected in GT6-infected subjects (0/5), but were detected in 1.1% (1/87), 3.8% (1/26), 6.7% (1/15), and 50.0% (1/2) of the GT1-, GT2-, GT4-, and GT5-infected subjects, respectively. NS5A polymorphisms (at positions 24, 28, 30, 31, 58, 92, or 93) were not detected in GT5-infected subjects (0/2), but were detected in 27.0% (24/89), 81.5% (22/27), 53.3% (8/15), and 42.9% (3/7) of the GT1-, GT2-, GT4-, and GT6-infected subjects, respectively. The presence of baseline polymorphisms did not impact treatment outcome with any HCV genotype in this study.

Summary/Conclusions (Continued)

Pharmacokinetic Results:

Pharmacokinetic exposures of ABT-493 and ABT-530 in HCV GT1-, 2-, 4-, 5-, or 6-infected subjects with cirrhosis were summarized. ABT-493 and ABT-530 concentrations quickly increased postdose to the maximum level at approximately 4 hours. There was no substantial drug accumulation for either ABT-493 or ABT-530 during the Treatment Period.

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). The majority of subjects who experienced AEs had events that were considered related to direct-acting antiviral agents. Few subjects experienced AEs ≥ Grade 3 in severity. Eleven subjects had serious AEs, none of which was considered related to direct-acting antiviral agent treatment. No subject had an AE leading to premature discontinuation of study drug.

One subject with a history of hemophilia died due to a nontreatment-emergent AE of cerebral hemorrhage considered not related to study drug 60 days after the last dose of study drug.

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 isolated values that were not clinically significant. One subject experienced an esophageal variceal bleed that was not associated with other clinical or laboratory evidence of decompensation.

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

Conclusions:

- In HCV GT1-, 2-, 4-, 5-, or 6-infected subjects with cirrhosis, a 12-week regimen of ABT-493/ABT-530 300 mg/120 mg QD achieved very high efficacy (SVR_{12} rate of 99.3%).
- As only one subject exhibited virologic relapse, no negative baseline predictors could be identified, including demographics, baseline HCV RNA level, genotype, presence of baseline polymorphisms, common comorbidities, or prior treatment history.
- Pharmacokinetic exposures of ABT-493 and ABT-530 in HCV GT1-, 2-, 4-, 5-, or 6-infected subjects with cirrhosis were summarized. ABT-493 and ABT-530 concentrations quickly increased postdose to the maximum level at approximately 4 hours. There was no substantial drug accumulation for either ABT-493 or ABT-530 during the Treatment Period.
- The fixed-dose combination of ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks was well tolerated and demonstrated a favorable safety profile.