2.0 Synopsis

<table>
<thead>
<tr>
<th>AbbVie Inc.</th>
<th>Individual Study Table Referring to Part of Dossier: Volume: Page:</th>
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</tr>
</thead>
</table>

**Name of Study Drug:** ABT-493 (glecaprevir)/ABT-530 (pibrentasvir)

**Name of Active Ingredient:** ABT-493/ABT-530

**Title of Study:** An Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Treatment-Naïve and Treatment-Experienced Asian Adults With Chronic Hepatitis C Virus Genotype (GT) 1 to GT6 Infection With Compensated Cirrhosis and With or Without Human Immunodeficiency Virus Co-Infection (VOYAGE-2)

**Coordinating Investigator:**

**Study Sites:** 34 sites in China and South Korea

**Publications:** 0

**Studied Period (Years):**
- First Subject First Visit: 29 September 2017
- Last Subject Last Visit: 15 November 2018 (for primary analysis)

**Phase of Development:** 3

**Objectives:**

The primary objectives of this study are to assess the efficacy (sustained virologic response 12 weeks post dosing, SVR$_{12}$ [HCV ribonucleic acid {RNA} < lower limit of quantification {LLOQ} 12 weeks after the last actual dose of study drug]) and safety following 12 or 16 weeks of treatment with the ABT-493/ABT-530 combination regimen in treatment-naïve (TN) or treatment-experienced (TE-PRS)$^a$ adults with chronic HCV GT1 – GT6-infection with compensated cirrhosis and with or without human immunodeficiency virus (HIV) co-infection.

The secondary objectives are to assess the percentage of subjects with on-treatment HCV virologic failure, the percentage of subjects with post-treatment (PT) relapse of HCV infection, and the percentage of HCV/HIV co-infected subjects achieving SVR$_{12}$.

An additional objective is to assess the pharmacokinetics of ABT-493 and ABT-530 in Asian HCV-infected adults.

$^a$TE-PRS: treatment-experienced with regimens containing interferon (IFN) (alpha, beta, or pegylated interferon [pegIFN]) with or without ribavirin (RBV), or sofosbuvir (SOF) with RBV with or without IFN.
Methodology:
Study M15-593 is an ongoing Phase 3, single-arm, open-label, multicenter study evaluating the efficacy, safety, and pharmacokinetics of ABT-493/ABT-530 in chronic HCV GT1 – GT6-infected Asian adult subjects who are HCV TN or TE-PRS, with compensated cirrhosis, and with or without HIV co-infection. Eligible subjects were enrolled and received ABT-493/ABT-530 300 mg/120 mg once daily (QD) for either 12 or 16 weeks. Treatment duration differed among subjects based on HCV GT and HCV treatment experience (12 weeks of treatment for GT1, 2, 3, 4, 5 and 6-infected subjects with the exception of 16 weeks for TE-PRS GT3-infected subjects).
During the PT Period, subjects who completed the Treatment Period, experienced on-treatment virologic failure, or otherwise prematurely discontinued the Treatment Period, are followed for 24 weeks to monitor safety and to evaluate efficacy and the emergence and/or persistence of HCV resistance-associated substitutions.

Number of Subjects (Planned and Analyzed):
Planned: approximately 160 subjects.
Analyzed: 160 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 Asian descent at least 18 years of age at time of screening.
- If female, either postmenopausal or permanently surgically sterile, or women of child-bearing potential practicing at least 1 protocol-specified method of birth control on or prior to Study Day 1 through at least 30 days after the last dose of study drug.
- Screening laboratory result indicating HCV GT1, 2, 3, 4, 5 or 6-infection.
- Subject had positive HCV antibody (Ab) and plasma HCV RNA viral load ≥ 1,000 IU/mL at screening visit.
- 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.
- HCV TN (had never received any approved or investigational HCV treatment) or TE-PRS. Previous HCV treatment must have been completed ≥ 8 weeks prior to screening.
- Compensated cirrhosis defined as Child-Pugh score of ≤ 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 exam, bleeding varices, use of diuretics for ascites, or hepatic encephalopathy.
- Documented as cirrhotic at any time previously or at Screening and absence of hepatocellular carcinoma (HCC) within 12 weeks prior to Screening or at Screening.

Main Exclusion Criteria:
- Female who was pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
- 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.
Diagnosis and Main Criteria for Inclusion (Continued):

- Positive test result at screening for hepatitis B surface antigen (HBsAg) or hepatitis B virus deoxyribonucleic acid (DNA) was detectable if HBsAg was negative.
- HCV genotyping performed during screening indicated coinfection with more than 1 HCV GT.
- Any cause of liver disease other than chronic HCV infection.
- Chronic HIV virus type 2 infection.
- 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 | AbbVie | Oral | Film-coated tablet | 100 mg/40 mg | 16-005216 |

Duration of Treatment:
Subjects received ABT-493/ABT-530 300 mg/120 mg QD for 12 or 16 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 or discontinuation of treatment.

**Resistance:**
For all subjects enrolled in South Korea who received study drug and experienced virologic failure, the HCV amino acid variants 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 subtype-specific reference sequence were to be analyzed. For GT1-infected subjects who enrolled in China, received study drug, and experienced virologic failure, the HCV amino acid variants at signature resistance-associated amino acid positions in NS3 and NS5A at baseline identified by population sequencing and comparison to the appropriate subtype-specific reference sequence were to be analyzed. In China, validated sequence analysis was available only for GT1.

The following resistance information was to be analyzed for subjects who received ABT-493/ABT-530, who experienced virologic failure, and who had an available post baseline sample with HCV RNA $\geq 1000$ IU/mL: 1) the amino acid substitutions in available post baseline samples based on comparison to the baseline sequence, 2) the amino acid substitutions in available post baseline samples at signature resistance-associated positions based on comparison to the appropriate subtype-specific reference sequence, and 3) the persistence of viral resistance.

**Pharmacokinetic:**
Individual plasma concentrations of ABT-493 and ABT-530 were tabulated and summarized for each subject, by visit, and for all subjects combined.

**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 variable was SVR\textsubscript{12} for the subjects in the intention-to-treat (ITT) population. The number and percentage of subjects achieving SVR\textsubscript{12} was presented along with a 2-sided 95% confidence interval (CI) for the percentage. The normal approximation to the binomial distribution was used to calculate the CI. No hypothesis was tested.

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 $\geq 100$ 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), and
- the percentage of subjects with PT relapse (defined as confirmed HCV RNA $\geq$ 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 reinfection), and
- the percentage of HCV/HIV co-infected subjects (determined at screening) who achieved SVR\textsubscript{12}.

For the analysis of relapse, a subject enrolled to receive 12 weeks of treatment was considered to have completed treatment if study drug duration was 77 days or more, and a subject enrolled to receive 16 weeks of treatment was considered to have completed treatment if study drug duration was 105 days or more.

The percentages of subjects with on-treatment HCV virologic failure, PT relapse, and SVR\textsubscript{12} were calculated along with 2-sided 95% Wilson score CIs.

In addition, a summary of reason for SVR\textsubscript{12} non-response (e.g., on-treatment virologic failure, relapse, reinfection) was provided for the set of all subjects and was to be provided for the set of HCV/HIV co-infected subjects.

**Subgroup:**

The percentage of subjects with SVR\textsubscript{12} was calculated for the set of all subjects in the ITT population for subgroups such as geographic region, prior HCV treatment history, type of previous regimen for TE-PRS subjects, interleukin 28B (IL28B) genotype, and baseline HCV RNA level. The 2-sided 95% Wilson score CI was produced if there were at least 10 subjects in the subgroup.

**Resistance:**

For subjects who enrolled in South Korea: The genes of interest for NGS were those encoding full length nonstructural viral protein 3/4A (NS3/4A) and NS5A. The following resistance analyses were to be 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. For subjects experiencing virologic failure, sequences at available postbaseline time points were compared to baseline and appropriate prototypic reference sequences to identify treatment-emergent substitutions.

For GT1-infected subjects who enrolled in China and experienced virologic failure: The genes of interest for population sequencing were those encoding amino acids 1 - 181 in NS3 and 1 - 251 in NS5A. For subjects experiencing virologic failure, sequences at available postbaseline time points were compared to baseline and appropriate prototypic reference sequences to identify treatment-emergent substitutions.
Statistical Methods (Continued)

HCV Genotype/Subtype:
For subjects enrolled in South Korea, phylogenetic analysis was conducted on all available HCV sequences from baseline samples in order to accurately determine HCV subtype.

Pharmacokinetic:
Individual plasma concentrations of ABT-493 and ABT-530 were tabulated and summarized for each subject, by visit and for all subjects combined.

Safety:
All subjects who received at least 1 dose of study drug were included in the safety analyses. Safety data were summarized for the set of all subjects and separately for the geographic region of China. Treatment-emergent adverse events (AEs) were defined as any event that began or worsened in severity after initiation of study drug through 30 days after the last dose of study drug. The number and percentage of subjects with treatment-emergent AEs were tabulated by primary Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and preferred term. Tabulations of the number of subjects with treatment-emergent AEs by severity grade (Grades 1 – 5) and relationship to study drug were also provided.

Mean changes in clinical laboratory and vital sign data from baseline to each post-baseline visit, including the Final Treatment Visit, were summarized descriptively. The number and percentage of subjects with post-baseline laboratory values meeting toxicity grades were summarized, as were subjects meeting criteria for assessment of hepatic laboratory values. The number and percentage of subjects with post-baseline vital sign values during the Treatment Period meeting pre-specified criteria for potentially clinically significant values were summarized.

Summary/Conclusions

Efficacy Results:
A total of 160 subjects were enrolled and all subjects received at least 1 dose of study drug. In China, 123 subjects were enrolled and all subjects received at least 1 dose of study drug.

SVR12 was achieved by 99.4% (159/160) of the GT1 – GT6 infected subjects, with a 2-sided 95% CI of 98.2% to 100.0%.

One subject (1/160 [0.6%]), an HCV GT3b-infected TN subject from China, experienced virologic failure; the subject relapsed at PT Week 4 and did not achieve SVR12.

High SVR12 rates were observed regardless of HCV GT, baseline IL-28B, baseline HCV RNA level, and prior treatment experience.
Summary/Conclusions (Continued)

Efficacy Results (Continued):

Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR\textsubscript{12})

(ITT Population – Imputation of Missing Data as Failures)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>All Subjects</th>
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<tbody>
<tr>
<td></td>
<td>N = 160</td>
</tr>
<tr>
<td>SVR\textsubscript{12}, n/N (%)</td>
<td>159/160 (99.4)</td>
</tr>
<tr>
<td>2-sided 95% CI\textsuperscript{a}</td>
<td>98.2, 100.0</td>
</tr>
<tr>
<td>Nonresponse, n/N (%)</td>
<td>1/160 (0.6)</td>
</tr>
<tr>
<td>Reason for nonresponse, n/N (%)</td>
<td></td>
</tr>
<tr>
<td>Virologic failure</td>
<td></td>
</tr>
<tr>
<td>On-treatment virologic failure</td>
<td>0/160</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>0/160</td>
</tr>
<tr>
<td>End-of-treatment failure</td>
<td>0/160</td>
</tr>
<tr>
<td>Relapse\textsubscript{12}</td>
<td>1\textsuperscript{c}/159\textsuperscript{d} (0.6)</td>
</tr>
<tr>
<td>Non-virologic failure</td>
<td></td>
</tr>
<tr>
<td>Premature study drug discontinuation</td>
<td>0/160</td>
</tr>
<tr>
<td>HCV reinfection\textsuperscript{b}</td>
<td>0/160</td>
</tr>
<tr>
<td>Missing SVR\textsubscript{12} data</td>
<td>0/160</td>
</tr>
<tr>
<td>Other</td>
<td>0/160</td>
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</tbody>
</table>

CI = confidence interval; GT = genotype; HCV = hepatitis C virus; IFN = interferon; ITT = intention-to-treat; pegIFN = pegylated interferon; QD = once daily; Relapse\textsubscript{12} = virologic relapse by Post-Treatment Week 12; RBV = ribavirin; = ribonucleic acid; SOF = sofosbuvir; SVR\textsubscript{12} = sustained virologic response 12 weeks post dosing; TE PRS = treatment-experienced with IFN (alpha, beta, or pegIFN) with or without RBV, or SOF with RBV with or without IFN

\textsuperscript{a} Calculated using the normal approximation to the binomial distribution.

\textsuperscript{b} Based on repeat genotype/subtype by central laboratory.

\textsuperscript{c} One subject, a 39-year-old HCV GT3b male from China, discontinued the study due to virologic failure (Relapse\textsubscript{12}) on PT Day 65. The subject had completed treatment.

\textsuperscript{d} Once subject from South Korea did not complete treatment, and therefore, was not included in the analysis of Relapse\textsubscript{12}. The subject achieved SVR\textsubscript{12}.

Study drug: ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks or 16 weeks

Note: GT3 TE-PRS subjects received 16 weeks of treatment; all other subjects received 12 weeks of treatment.

Other Notes: 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.
Summary/Conclusions (Continued)

Efficacy Results (Continued):

Among subjects enrolled in China, SVR\textsubscript{12} was achieved in 99.2\% (122/123) of the GT1 – GT6-infected subjects, with a 2-sided 95\% CI of 95.5\% to 99.9\%.

Virologic Response (SVR\textsubscript{12}) Among Subjects in China (ITT Population – Imputation of Missing Data as Failures)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>China N = 123</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR\textsubscript{12}, n/N (%)</td>
<td>122/123 (99.2)</td>
</tr>
<tr>
<td>2-sided 95% CI\textsuperscript{a}</td>
<td>95.5, 99.9</td>
</tr>
<tr>
<td>Nonresponse, n/N (%)</td>
<td>1/123 (0.8)</td>
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Reason for nonresponse, n/N (%):

<table>
<thead>
<tr>
<th>Reason for nonresponse</th>
<th>n/N (%)</th>
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<tr>
<td>Virologic failure</td>
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</tr>
<tr>
<td>Missing SVR\textsubscript{12} data</td>
<td>0/123</td>
</tr>
<tr>
<td>Other</td>
<td>0/123</td>
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CI = confidence interval; GT = genotype; HCV = hepatitis C virus; IFN = interferon; ITT = intention-to-treat; pegIFN = pegylated interferon; QD = once daily; Relapse\textsubscript{12} = virologic relapse by Post-Treatment Week 12; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR = sustained virologic response; SVR\textsubscript{12} = sustained virologic response 12 weeks postdosing; TE PRS = treatment-experienced with IFN (alpha, beta, or pegIFN) with or without RBV, or SOF with RBV with or without IFN

\textsuperscript{a} Calculated using the Wilson score method.

\textsuperscript{b} Based on repeat genotype/subtype by central laboratory.

\textsuperscript{c} One subject, a 39-year-old HCV GT3b male, discontinued the study due to virologic failure (Relapse\textsubscript{12}) on PT Day 65. The subject had completed treatment.

Study drug: ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks or 16 weeks

Note: GT3 TE-PRS subjects received 16 weeks of treatment; all other subjects received 12 weeks of treatment.

Other Notes: 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.
Summary/Conclusions (Continued)

Resistance Results:
Based on phylogenetic analysis of NS3/4A or NS5A sequences from 37 subjects enrolled in South Korea, 2 subtypes were identified in the study, including 23 (62.2%) GT1b and 14 (37.8%) GT2a-infected subjects. Among subjects enrolled in South Korea, baseline polymorphisms at the key subset of amino acid positions in NS3 (positions 155, 156, or 168) were not detected. Baseline NS5A polymorphisms (at positions 24, 28, 30, 31, 58, 92, or 93) were detected in 52.2% (12/23) and 85.7% (12/14) of the GT1b- and GT2a-infected subjects, respectively. Of note, Y93H was detected in 21.7% (5/23) of the GT1b-infected subjects. The high prevalence of NS5A polymorphisms in GT2a was due to the common M31 polymorphism.
None of the GT1- or GT2-infected subjects enrolled in South Korea experienced virologic failure, indicating that the baseline polymorphisms had no impact on treatment outcome.

Pharmacokinetic Results:
Binned plasma concentrations of ABT-493 and ABT-530 following administration of ABT-493/ABT-530 300 mg/120 mg in Asian adults with chronic HCV GT1 – GT6 infection and compensated cirrhosis during treatment were summarized by time interval. ABT-493 and ABT-530 concentrations quickly increased post dose to the maximum level by approximately 4 hours. Steady-state plasma concentrations were attained by Day 7, and there was minimal drug accumulation for ABT-493 and ABT-530 during the treatment period.

Safety Results:
The fixed-dose combination of ABT-493/ABT-530 300 mg/120 mg QD administered for 12 weeks or 16 weeks (the latter for GT3 TE-PRS subjects) was well tolerated and demonstrated a favorable safety profile in HCV GT1 – GT6-infected subjects with compensated cirrhosis. Approximately half of the subjects who experienced AEs had events with a maximum severity of Grade 1 (mild). The most common events (≥ 5.0% of subjects) were upper respiratory tract infection and urinary tract infection. Of those reporting upper respiratory tract infection or urinary tract infection, all except 1 event of upper respiratory tract infection were assessed as not related to the study drug.
Serious AEs were infrequent (occurring in 3.1% of subjects). Of these, 1 subject (from China) experienced an SAE which was considered DAA-related by the investigator: a Grade 1 (mild) AE of upper gastrointestinal hemorrhage that did not lead to interruption or discontinuation of study drug. No treatment-emergent AEs of death were reported. One subject (from China) died on PT Day 172 as a result of an SAE of gastrointestinal hemorrhage; the event was not considered to be related to study drug by the investigator, but related to liver cirrhosis, with hematemesis reported as the primary cause of death.
One subject (from South Korea) experienced a Grade 3 nonserious AE of blood bilirubin increased, which was not considered related to study drug by the investigator, and led to premature drug discontinuation at Day 49; the subject achieved SVR12.
No subject experienced drug-induced liver injury. One treatment-emergent hepatic decompensation/hepatic failure event was identified in 1 subject (from China) who experienced a nonserious, Grade 1 event of ascites, with onset on PT Day 2, which was not considered DAA-related by the investigator. The event resolved by PT Day 40. This subject achieved SVR12.
Laboratory abnormalities were infrequent and not clinically relevant. No safety signal was identified.
**Summary/Conclusions (Continued)**

**Discussion and Overall Conclusions:**

- In chronic HCV GT1 – GT6-infected Asian subjects with compensated cirrhosis, a 12- or 16-week regimen of ABT-493/ABT-530 300 mg/120 mg QD achieved high efficacy.
  - SVR<sub>12</sub> rate for all subjects was 99.4%.
  - SVR<sub>12</sub> rate for subjects from China was 99.2%.
  - No subject experienced on-treatment virologic failure.
  - One HCV GT3b-infected TN subject from China relapsed at PT Week 4 and did not achieve SVR<sub>12</sub>.
  - High SVR<sub>12</sub> rates were observed regardless of HCV GT, baseline IL-28B, baseline HCV RNA level, and prior treatment experience.

- None of the GT1- or GT2-infected subjects enrolled in South Korea experienced virologic failure, indicating that baseline polymorphisms had no impact on treatment outcome.

- ABT-493 and ABT-530 concentrations quickly increased post dose to the maximum levels at approximately 4 hours. Steady-state plasma concentrations were attained by Day 7, and there was minimal drug accumulation for ABT-493 and ABT-530 during the treatment period.

- The fixed-dose combination of ABT-493/ABT-530 300 mg/120 mg QD was well tolerated and demonstrated a favorable safety profile.