

## Synopsis

<b>AbbVie Inc.</b>	<b>Individual Study Table Referring to Part of Dossier:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> No AbbVie Investigational Product was administered	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> No AbbVie Investigational Product was administered	<b>Page:</b>	
<b>Title of Study:</b> A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy (ABT-493 and/or ABT-530) in Subjects Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection		
<b>Coordinating Investigator:</b> ██████████, MD		
<b>Study Sites:</b> 42 sites in 7 countries (Australia, Belgium, Canada, Germany, New Zealand, United Kingdom, and United States, including its territory Puerto Rico).		
<b>Publications:</b> 1 abstract		
<b>Studied Period (Years):</b> First Subject First Visit: 22 June 2015 Last Subject Last Visit: 15 October 2019	<b>Phase of Development:</b> 2/3	
<p><b>Objectives:</b></p> <p>The primary objectives were: to assess the durability of response for subjects who achieved sustained virologic response 12 weeks post dosing (SVR<sub>12</sub>) with a regimen including ABT-493 and/or ABT-530; to assess the persistence of specific hepatitis C virus (HCV) amino acid variants associated with drug resistance in subjects who experienced virologic failure (VF).</p> <p>The secondary objectives were: to summarize medical events related to progression of liver disease including but not limited to events of hepatic decompensation, change in Child-Pugh classification, liver transplantation, hepatocellular carcinoma, and/or death; to summarize results of the following laboratory tests and scores: FibroTest, aspartate aminotransferase to platelet ratio index (APRI), inducible protein 10 (IP-10), alpha fetoprotein (if collected under a previous protocol version), FibroScan, and liver biopsy.</p>		
<p><b>Methodology:</b></p> <p>Study M13-576 was a Phase 2/3, multicenter, rollover study to assess resistance and durability of response to ABT-493 and/or ABT-530 in subjects who had participated in Phase 2 or 3 clinical studies with these agents for the treatment of chronic HCV. No AbbVie study drug was administered in this study. Participation in Study M13-576 was offered to subjects who received at least one dose of an ABT-493- and/or ABT-530-containing regimen at any dose level in an eligible prior AbbVie Phase 2 or 3 study for the treatment of chronic HCV and elected to enroll in this study. The subject must have completed the follow-up period of the prior eligible AbbVie study. An attempt was to be made to enroll all VFs who did not receive immediate re-treatment with a regimen containing ABT-493/ABT-530.</p>		

**Methodology (Continued):**

Subjects were followed for a total of approximately 3 years after their last dose of direct-acting antiviral agent (DAA) in the previous HCV clinical study. The 3 years were inclusive of any post-treatment period in the prior study, as well as any gaps between the end of the prior study and enrollment in this study. Subjects must have completed the full post-treatment period of the prior study before enrolling into Study M13-576. Once a subject had reached 3 years post-DAA therapy, participation in this study was completed, except for subjects enrolled with VF who received re-treatment with an HCV antiviral regimen other than investigational ABT-493/ABT-530. Subjects who were re-treated with investigational ABT-493/ABT-530 were not allowed in this study. Subjects who were re-treated with HCV regimens other than investigational ABT-493/ABT-530 had only 1 further assessment for treatment outcome 12 weeks after stopping that therapy or earlier if already known (in cases of treatment failure).

Subjects who had not been re-treated returned to the study site for their scheduled visits on an outpatient basis until approximately 3 years after their last dose of DAA in the previous clinical study.

Some of the study visits and visit activities (including but not limited to clinical laboratory tests and concomitant medication assessment) may have been optionally conducted in the home or non-hospital/clinic environment as arranged by the Investigator with the agreement of the subject, and with the prior approval of the sponsor.

**Number of Subjects (Planned and Analyzed):**

Planned: approximately 400 subjects.

Analyzed: 384 subjects were enrolled and 377 subjects were included in the full analysis set (FAS).

**Diagnosis and Main Criteria for Inclusion:**

Inclusion criteria: male or female 18 years of age or older who had received at least one dose of an ABT-493- and/or ABT-530-containing regimen in an eligible prior AbbVie HCV Phase 2 or 3 study; the interval between the last dose of the ABT-493 and/or ABT-530 therapy from the previous clinical study and enrollment in Study M13-576 must have been no longer than 2 years for subjects who had not been re-treated. Subjects who had been treated with a commercially available anti-HCV treatment could be enrolled more than 2 years after the last dose of the ABT-493 and/or ABT-530 therapy from the previous clinical study. The subject must have completed the post-treatment period of an eligible prior study and signed and date the informed consent form approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) prior to the initiation of any study-specific procedures.

Exclusion criteria: the investigator considered the subject unsuitable for the study for any reasons (e.g., failure to comply with study procedures in the prior AbbVie clinical study); receipt of any investigational HCV antiviral treatment after receiving ABT-493 and/or ABT-530 in the prior study; subjects who experienced non-virologic treatment failure due to premature discontinuation of study drug in the prior study of ABT-493 and/or ABT-530; participation in AbbVie's Study M15-942 for re-treatment for VFs following the prior Phase 2 or 3 study.

**Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:**

No AbbVie study drug was administered in this study.

**Duration of Treatment:**

No AbbVie study drug was administered in this study (as above). Subjects were followed for a total of approximately 3 years after their last dose of DAA in the previous HCV clinical study.

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

Not applicable.

**Criteria for Evaluation**

**Efficacy:**

The primary efficacy outcome variables were: the percentage of subjects who maintained sustained virologic response (SVR) out of those who achieved SVR<sub>12</sub> in the prior study with an ABT-493- and/or ABT-530-containing regimen; the percentage of subjects who relapsed or had new HCV infection at any time up to the last follow-up in this study out of subjects who achieved SVR<sub>12</sub> in the previous study and enrolled in this study.

A plasma sample for HCV ribonucleic acid (RNA) levels was collected until the end of the study or initiation of re-treatment for HCV (if applicable). Plasma HCV RNA levels were determined for each sample collected by the central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. The lower limit of detection (LLOD) and lower limit of quantification (LLOQ) for this assay (regardless of genotype [GT]) were both 15 IU/mL. If a subject's HCV RNA level changed from < LLOQ to ≥ LLOQ during the study, confirmatory testing was to be completed as soon as possible but no later than 2 weeks after the study visit corresponding with the possible HCV RNA relapse.

The primary resistance outcome variables were: the persistence of resistance-associated amino acid variants assessed by population and/or deep sequencing for a period up to 3 years after the subject's last dose of DAA therapy in the prior AbbVie clinical study. A plasma sample for HCV resistance testing was collected at the study visits for all subjects, until the end of the study or initiation of re-treatment for HCV (if applicable).

The clinical variables (secondary outcomes) were: variables related to liver disease progression, monitored and summarized as described in the study procedures, including but not limited to events indicative of hepatic decompensation; changes in Child-Pugh classification; liver transplantation; hepatocellular carcinoma; and death. Results of the following laboratory tests and studies were summarized: IP-10, FibroTest, APRI, alpha fetoprotein (if collected under a previous protocol version) FibroScan, liver biopsy. FibroScan and liver biopsy were not performed as study procedures, but any available results from source documents were summarized.

**Safety:**

The following safety evaluations were performed during the study: assessment of medical events related to liver disease/HCV infection, assessment of SAEs related to study procedures or to exposure to ABT-493 and/or ABT-530 in the prior study, laboratory test assessments, and liver ultrasound or other liver imaging.

### **Statistical Methods**

There was no randomization, blinding, or control groups in this study. No quantitative analyses or tests of statistical significance were planned; statistical analyses were purely descriptive.

The final analysis was conducted when all subjects enrolled in the study had completed the follow-up period. Analyses were performed using SAS<sup>®</sup> Version 9.4 (SAS Institute, Inc., Cary, NC) or later under the UNIX operating system. All demographic, efficacy, and safety analyses were conducted on all subjects who enrolled in this study without receiving re-treatment prior to enrolling in this study, denoted as the full analysis set (FAS). Subjects who were VFs who received re-treatment prior to enrollment in this study were summarized separately and were excluded from the FAS.

#### **Efficacy:**

Efficacy analyses were conducted on the FAS, including data up to the last follow-up in this study prior to any HCV re-treatment. The number and percentage of subjects in the FAS who maintained SVR in this study was summarized out of subjects in the FAS who achieved SVR<sub>12</sub> in the previous study. The number and percentage of subjects who relapsed or had new HCV infection were summarized out of subjects in the FAS who achieved SVR<sub>12</sub> in the previous study. The time to relapse or new infection from the end of DAA treatment for subjects who achieved HCV RNA < LLOQ at the end of treatment in the previous study was displayed graphically using Kaplan Meier curves. Similarly, the time to relapse or new infection from SVR<sub>12</sub> time point for the subset of subjects who achieved SVR<sub>12</sub> in the previous study was also displayed graphically using Kaplan-Meier curves. These summaries were separate for subjects who had probable relapse as distinguished from subjects who had probable new HCV infection based on AbbVie's evaluation of DNA sequence of HCV drug target genes.

For subjects in the FAS, HCV RNA measurements taken after the start of another anti-viral HCV treatment (after completion of AbbVie DAA treatments in previous study) were excluded from the analyses. For both subjects in the FAS and subjects excluded from the FAS, a listing of subjects who were re-treated was provided summarizing HCV treatment regimen and SVR outcome.

#### **Resistance:**

The following subjects in the FAS had resistance testing conducted if samples were available: (1) those with on-treatment VF in the previous study; (2) those with post-treatment relapse prior to enrollment in Study M13-576; and (3) those who became viremic (with HCV) during Study M13-576.

#### **Safety:**

Safety analyses were presented for subjects in the FAS. As this was a non-drug interventional study, only SAEs that the investigator considered reasonably related to interventional study procedures (i.e., venipunctures) or those considered reasonably related to ABT-530 and/or ABT-493 drug exposure in the prior study by the investigator were reported as serious adverse events. Serious adverse event data were to be summarized and presented using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). A summary of SAEs by SOC and PT was to be generated. Listings of all serious (as defined in the protocol) adverse events and deaths (from the time the subject signed the study-specific informed consent through the end of the study) were to be provided.

### **Statistical Methods (Continued)**

#### **Safety (continued):**

Documentation of any significant changes in the medical history related to liver disease and/or HCV infection that were considered to be clinically significant by the investigator and occurred since the completion of the prior AbbVie clinical study were collected at the Day 1 Visit and recorded on the appropriate Medical Events electronic case report form (eCRF) for all subjects, except for those subjects entering the study on a re-treatment regimen. For subjects entering the study on a re-treatment regimen, this information was collected for changes that occurred since the prior AbbVie clinical study but before the start of the re-treatment regimen only. In addition, history of past HCV drug treatment during the prior study and before the prior study was collected at the Day 1 Visit.

Any events related to liver disease progression and/or HCV infection considered to be clinically significant by the investigator and that began or worsened after Day 1 were captured on the appropriate Medical Events eCRF(s).

Significant events related to liver disease progression included but were not limited to: the development of cirrhosis, events indicative of hepatic decompensation, changes in Child-Pugh classification, liver transplantation, hepatocellular carcinoma, and/or death.

The number and percentage of subjects who reported each and any of the following medical events was summarized: development of cirrhosis; hepatic decompensation (including variceal bleeding, new ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepato-renal syndrome, hepatic hydrothorax, and other evidence of hepatic decompensation); change in the Child-Pugh category, hepatocellular carcinoma; occurrence of liver transplantation; death; and other.

Listings of each medical event were provided. In addition, listings of any liver diagnostic testing that was collected (e.g., liver biopsy or FibroScan scores) were provided.

Data collected from the central and local laboratories, including additional laboratory testing due to an SAE, were used in all analyses. Each protocol-specified laboratory parameter was summarized at each applicable study visit (e.g., Day 1, Month 3, Month 6, etc., as defined in the protocol) with the sample size, visit mean, standard deviation, minimum, median, and maximum.

### **Summary/Conclusions**

#### **Efficacy Results:**

A total of 384 subjects were enrolled and 287 subjects completed the study. The median duration of follow up was 35.5 months.

#### Durability of Sustained Virologic Response

In the prior studies overall, 376/377 subjects (99.7%) had achieved SVR<sub>12</sub>.

One subject from Study M15-410 who was included in the FAS, did not achieve SVR<sub>12</sub> in the prior study. The subject was a 59-year-old male, HCV GT1a, cirrhotic and treatment-experienced (ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin) who had received ABT-493/ABT-530 300 mg/120 mg QD for 16 weeks and experienced on-treatment VF.

**Summary/Conclusions (Continued)**

**Efficacy Results (Continued):**

Among those who had achieved SVR<sub>12</sub> in the prior studies, a total of 374/376 subjects (99.5%) maintained SVR in the current study.

Two subjects who had previously achieved SVR<sub>12</sub> in the prior study did not maintain SVR:

- One subject from Study M14-868, a 61-year-old white female experienced reinfection 191 days after the last dose of prior study drug (ABT-493/ABT-530 300 mg/120 mg QD for 16 weeks). The subject was infected with HCV GT3a at baseline and achieved SVR<sub>12</sub> but was determined to be infected with HCV GT1a at the Post-Treatment Week 24 time point as a result of contact with an infected individual.
- One subject from Study M15-410, a 58-year-old white male with HCV GT1b and compensated cirrhosis experienced a late relapse 390 days (Post-Treatment Week 60) after the last dose of prior study drug (ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks). The subject had failed on DCV and interferon (alpha, beta, or pegylated interferon) with or without ribavirin (PR) prior to enrolling in Study M15-410. The subject withdrew consent and prematurely discontinued from the study after learning he had relapsed 1 week prior to the first study visit.

Subjects who had been re-treated

Among all enrolled subjects, 4 subjects received HCV re-treatment; these were subjects who experienced VF in the previous study. One subject from Study M14-868, a 59-year-old white male with HCV GT3a who had been treated with ABT-493/ABT-530 300 mg/120 mg QD for 16 weeks in the prior study, was re-treated with sofosbuvir/velpatasvir (SOF/VEL) + ribavirin (RBV), and did not achieve SVR<sub>12</sub> after re-treatment (no known cause of relapse). All other subjects achieved SVR<sub>12</sub> after re-treatment.

**Resistance Results:**

Persistence of Specific HCV Amino Acid Substitutions Associated with Drug Resistance in Subjects Who Experienced Virologic Failure

Persistence of substitutions at signature amino acid positions in nonstructural viral protein 3 (NS3) and nonstructural viral protein 5A (NS5A) was followed for 1 GT1a-infected who had experienced VF in Study M15-410. This subject had substitutions Y56H, R155T, D168A, and the Q80K polymorphism at the time of enrollment into this study. All these NS3 substitutions as well as D168T remained detectable at similar prevalence within the subject's viral population at the Month 3, 6, and 12 visits. In NS5A, substitutions M28T, Q30H, H58D, and Y93H were detectable at the time of enrollment in this study as well as at the Month 3, 6, and 12 visits at a similar prevalence within the subject's viral population. This subject subsequently achieved SVR<sub>12</sub> on a SOF/VEL/voxilaprevir (VOX) regimen.

**Summary/Conclusions (Continued)**

**Safety Results:**

Seven subjects were reported with medical events related to progression of liver disease or HCV infection: 5 subjects were reported with medical events of hepatocellular carcinoma (HCC; none of the events were considered related to ABT-493/ABT-530 by the investigator); 1 subject was reported with an event of regenerated node in the liver; 1 subject was initially diagnosed with unconfirmed HCC and was later diagnosed with cholangiocarcinoma/differentiated adenocarcinoma.

There were no events of development of cirrhosis, liver decompensation, change in Child-Pugh classification in a subject with cirrhosis, or liver transplantation.

One subject died as a result of metastatic cancer of unknown origin; this event did not meet the criteria for a protocol-defined medical event.

**Conclusions:**

- Among those who had achieved SVR<sub>12</sub> in the prior studies, a total of 374/376 subjects (99.5%) maintained SVR in the current study.
- Although the resistance analysis only included one DAA-experienced subject, results in this subject indicate persistence of resistance-associated amino acid substitutions in both NS3 and NS5A, perhaps due to undetectable levels of wild-type virus at the time of failure preventing outgrowth of wild-type or the fitness of the combination of substitutions; however, the subject achieved SVR<sub>12</sub> on a subsequent SOF/VEL/VOX regimen.
- Five subjects were reported with medical events of HCC; 1 subject was reported with an event of regenerated node in the liver, 1 subject was initially diagnosed with unconfirmed HCC and was later diagnosed with cholangiocarcinoma/differentiated adenocarcinoma. There were no events of development of cirrhosis, liver decompensation, change in Child-Pugh classification in a subject with cirrhosis, or liver transplantation.
- One subject died as a result of metastatic cancer of unknown origin; this event did not meet the criteria for a protocol-defined medical event.

**Date of Report:** 04Jun2020