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 Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus Genotype 1 Infection (ENDURANCE-1)		
Coordinating Investigator: [redacted]		
Study Sites: 115 sites in Australia, Austria, Belgium, Canada, Chile, France, Germany, Hungary, Israel, Italy, Korea, Lithuania, Mexico, New Zealand, Poland, Portugal, Romania, Spain, Sweden, Switzerland, Taiwan, United Kingdom, and the United States (and its territory, Puerto Rico)		
Publications: 1 abstract		
Studied Period (Years): First Subject First Visit: 21 October 2015 Last Subject Last Visit for Primary Analysis: 09 September 2016	**Phase of Development:** 3	

Objectives:

The primary objectives were to show the noninferiority of the sustained virologic response 12 weeks postdosing (SVR_{12}) rates among monoinfected hepatitis C virus (HCV) genotype 1 (GT1) direct-acting antiviral agent (DAA)-naïve subjects (the percentage of subjects achieving SVR_{12}, [HCV RNA < lower limit of quantitation (LLOQ) 12 weeks following therapy]) of 12 weeks of treatment with the combination regimen ABT-493/ABT-530 to the historical sustained virologic response rate (SVR) rate established by current approved standard of care regimens for monoinfected HCV GT1 DAA-naïve subjects (ombitasvir [OBV]/paritaprevir [PTV]/ritonavir [r] + dasabuvir [DSV] ± ribavirin [RBV] or sofosbuvir [SOF]/ledipasvir [LDV] for 12 weeks); to show the noninferiority in SVR_{12} rates among monoinfected HCV GT1 DAA-naïve subjects of the ABT-493/ABT-530 regimen for 8 weeks versus 12 weeks of treatment; and to assess the safety of 8 and 12 weeks of treatment with the combination regimen ABT-493/ABT-530.

The secondary objectives were to assess the percentage of subjects with SVR_{12} among monoinfected HCV GT1 subjects; the percentage of subjects with SVR_{12} among all HCV GT1 subjects; the percentage of subjects with SVR_{12} among subjects with HCV GT1/human immunodeficiency virus-1 (HIV-1) coinfection; the percentage of subjects with SVR_{12} among prior SOF treatment-experienced HCV GT1 subjects; the percentages of subjects with on-treatment virologic failure; and the percentages of subjects with post-treatment relapse.

Methodology:

This was a Phase 3, randomized, open-label, multicenter study to evaluate the efficacy and safety of the ABT-493/ABT-530 combination regimen in HCV treatment-naïve or prior treatment-experienced (i.e., interferon [IFN] or pegylated interferon [pegIFN] with or without RBV, or SOF plus RBV with or without pegIFN) chronic HCV GT1-infected or HCV GT1/HIV-1 coinfected subjects without cirrhosis for 8- and 12-week treatment durations.

Hepatitis C virus GT1-infected treatment-naïve or prior treatment-experienced subjects without cirrhosis were randomized in a 1:1 ratio into 1 of 2 treatment arms (310 subjects per arm):

- Arm A: ABT-493/ABT-530 (300 mg/120 mg once daily [QD]) for 12 weeks;
- Arm B: ABT-493/ABT-530 (300 mg/120 mg QD) for 8 weeks.

Randomization was stratified by screening viral load (< or ≥ 6 million IU/mL) and by HCV GT1 subtype (1b or non-1b).

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, plasma HIV-1 RNA (if applicable), HIV resistance (if applicable), and the emergence and/or persistence of HCV resistance-associated viral variants.

Number of Subjects (Planned and Analyzed):

Planned: approximately 620 subjects

Analyzed: 703 subjects (352 in Arm A and 351 in Arm B) were randomized 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) at least 18 years of age at time of screening.
- Screening laboratory result indicating HCV GT1 infection.
- Positive anti-HCV antibody and plasma HCV RNA viral load ≥ 1,000 IU/mL at the 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; or
  - Abnormal alanine aminotransferase levels for at least 6 months before screening.
- Hepatitis C virus treatment-naïve or HCV treatment-experienced (has failed prior IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN therapy).
- Documented as noncirrhotic

In addition, subjects enrolled with HCV GT1 and HIV-1 coinfection must have also met the following criteria per local standard practice:

- Positive test result for anti-HIV antibody at screening.
- Naïve to treatment with any antiretroviral treatment (ART) regimen (and had no plans to initiate ART while participating in this study) or on a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to 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.
- 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.
- 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.
- Failed a previous regimen containing HCV protease inhibitors and/or nonstructural viral protein 5A (NS5A) inhibitors.
- Chronic HIV-2 infection.

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

Investigational Product	Manufacturer	Dosage Form/Mode of Administration	Bulk Lot Number
ABT-493/ABT-530	AbbVie	100 mg/40 mg tablet/Oral	15-005089 15-006020 15-006595

Duration of Treatment:

Subjects in Arm A received ABT-493/ABT-530 for 12 weeks.

Subjects in Arm B received ABT-493/ABT-530 for 8 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 HCV variants in available samples at signature amino acid positions in nonstructural viral protein 3 (NS3) and NS5A at baseline identified by next-generation sequencing (NGS) and comparison to the appropriate prototypic reference sequences 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 postbaseline sample with HCV RNA $\geq$ 1,000 IU/mL: 1) the HCV amino acid variants in available postbaseline samples identified by NGS, and comparison to the baseline sequences, 2) the HCV amino acid variants in available postbaseline samples at signature positions identified by NGS and comparison to the appropriate prototypic reference sequences, and 3) the persistence of HCV viral resistance by NGS.

If any HCV GT1/HIV-1 coinfected subject developed HIV-1 RNA $\geq$ 20 copies/mL at 1 assessment and $\geq$ 500 copies/mL on repeat testing after starting the study, the HIV-1 protease, reverse transcriptase, and integrase sequences, as applicable, were analyzed.

Pharmacokinetics:

Plasma concentrations and pharmacokinetic parameter values for ABT-493 and ABT-530 were tabulated for each subject and arm. Summary statistics were computed for each time and visit.

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 < LLOQ 12 weeks after the last actual dose of study drug). The 3 ranked primary efficacy endpoints were:

- Efficacy of the 12-week treatment duration (Arm A): lower bound of the 2-sided 95% confidence interval for the percentage of subjects in Arm A achieving SVR_{12} is greater than 91% in the ITT-PS population (the intention-to-treat [ITT] subset of HCV monoinfected DAA-naïve subjects).
- Noninferiority of the 8-week treatment duration (Arm B) to Arm A in SVR_{12} using a noninferiority margin of 5% in the per protocol (PP) ITT-PS population (ITT-PS-PP) (all randomized subjects in the ITT-PS population, with the exception of subjects who prematurely discontinued prior to Week 8, subjects who experienced virologic failure prior to Week 8, and subjects who had no HCV RNA value in the SVR_{12} visit window or later).
- Noninferiority of the 8-week treatment duration (Arm B) to Arm A in SVR_{12} using a noninferiority margin of 5% in the ITT-PS population.

In order to control the Type I error rate, a fixed sequence testing procedure was used for the ranked primary efficacy endpoints. Only if success had been demonstrated for the first primary endpoint did the testing proceed to the second primary endpoint. Similarly, only if success had been demonstrated for the second primary endpoint did the testing proceed to the third primary endpoint.

The following secondary endpoints were summarized outside the fixed-sequence testing procedure and were:

- The percentage of subjects with SVR_{12} in the ITT-MS population (ITT monoinfected HCV GT1 subjects);
- The percentage of subjects with SVR_{12} in the ITT population;
- The percentage of subjects with SVR_{12} among subjects with HCV GT1/HIV-1 coinfection;
- The percentage of subjects with SVR_{12} among prior SOF-treatment experienced HCV GT1 subjects;
- 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); and
- 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; excluding subjects who had been shown to be reinfected).

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 NS5A. The following resistance information was analyzed for baseline samples from all subjects separated by subtype, study arm, and prior treatment experience: 1) the variants at signature amino acid position at baseline identified by NGS were compared to the appropriate prototypic reference sequence; and (2) comparison of SVR_{12} rates in subjects with or without baseline variants was conducted.

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} was presented for subgroup variables, such as HCV GT1/HIV-1 coinfection, baseline viral load, prior treatment experience, or HCV GT1 subgenotype.

Pharmacokinetics:

Plasma concentrations of ABT-530 and ABT-493 and pharmacokinetic parameter values for ABT-493 and ABT-530 were tabulated for each subject and arm. Summary statistics were computed for each time for intensive pharmacokinetic collection days.

Safety:

All subjects who received at least 1 dose of study drugs 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 and compared between arms using Fisher's exact test. 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 from baseline in laboratory tests and vital signs to each postbaseline visit were summarized and differences between treatment groups were to be analyzed using contrasts within an analysis of variance model, as appropriate. The number and percentage of subjects with postbaseline values meeting toxicity grades and meeting potential hepatotoxicity criteria were summarized. Frequencies and percentages of subjects with postbaseline values meeting predefined criteria for potentially clinically significant vital sign values were summarized and compared between arms using Fisher's exact tests.

Summary/Conclusions

Efficacy and Resistance Results:

Efficacy

The following 3 ranked primary efficacy endpoints were assessed:

- The first primary efficacy endpoint was achieved. Noninferiority of the 12-week arm to the historical control was demonstrated, as the 95% lower confidence bound (LCB) for SVR_{12} in the ITT-PS population was > 91%.
- The second primary endpoint was achieved. Noninferiority of the 8-week arm to the 12-week arm was demonstrated in the ITT-PS-PP population, as the 95% LCB for difference in SVR_{12} rates was > –5%.
- The third primary endpoint was achieved. Noninferiority of the 8-week arm to the 12-week arm was demonstrated in the ITT-PS population, as the 95% LCB for difference in SVR_{12} rates was > –5%.

Summary/Conclusions (Continued)

Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR_{12}) (ITT-PS and ITT-PS-PP Populations)

	ITT-PS[a]		ITT-PS-PP[b]	
Assessment	**Arm A N = 332**	**Arm B N = 335**	**Arm A N = 331**	**Arm B N = 332**
SVR_{12}, n/N (%)	331/332 (99.7)	332/335 (99.1)	331/331 (100)	332/332 (100)
95% CI[c]	99.1, 100.0	98.1, 100	98.9, 100.0	98.9, 100.0
Treatment difference[d] (95% CI)	–0.6 (–1.8, 0.6)		0.0 (–1.1, 1.1)	
Noninferiority threshold	–5%		–5%	
Nonresponders, n/N (%)	1/332 (0.3)	3/335 (0.9)	0/331	0/332
Reason for nonresponse, n/N (%)				
Virologic failure	0/332	1/335 (0.3)	0/331	0/332
On-treatment virologic failure	0/332	1/335 (0.3)	0/331	0/332
Relapse	0/332	0/333	0/331	0/332
Non-virologic failure	1/332 (0.3)	2/335 (0.6)	0/331	0/332
Premature study drug discontinuation	0/332	1/335 (0.3)	0/331	0/332
HCV reinfection	0/332	0/335	0/331	0/332
Missing SVR_{12} data[c]	1/332 (0.3)	1/335 (0.3)	0/331	0/332
Other	0/332	0/335	0/331	0/332
Threshold based on historic 3-DAA ± RBV regimen-based or SOF/LDV-based SVR rates (ITT-PS)				
Noninferiority threshold	91%			

Arm A: ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks

Arm B: ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks

3-DAA = 3 direct-acting antiviral agents (ombitasvir/paritaprevir/ritonavir + dasabuvir); CI = confidence interval; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; ITT = intention-to-treat; LDV = ledipasvir; QD = once daily; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR = sustained virologic response; SVR_{12} = sustained virologic response 12 weeks postdosing

a. ITT-PS = ITT subset of HCV monoinfected DAA-naïve subjects.

b. ITT-PS-PP = ITT-PS excluding subjects who prematurely discontinued prior to Week 8 (subjects with treatment duration < 52 days), subjects who experienced virologic failure prior to Week 8 (subjects with on-treatment virologic failure before Day 52), subjects without virologic failure who had no HCV RNA value in the SVR_{12} visit window or later, and subjects who are SVR_{12} nonresponders due to reinfection.

c. Calculated using the normal approximation to the binomial distribution Wilson's score method, unless the rate is 100%, in which case the Wilson's score method was used instead.

d. SVR_{12} rate in 8-week treatment group (Arm B) minus SVR_{12} rate in 12-week treatment group (Arm A).

Summary/Conclusions (Continued)

Results for secondary efficacy endpoints are shown below.

Secondary Efficacy Endpoint Results (ITT and ITT-MS Populations)

Assessment	Arm A	Arm B
SVR_{12}, n/N (%)		
ITT-MS population	333/334 (99.7)	333/336 (99.1)
ITT population	351/352 (99.7)	348/351 (99.1)
Subjects with HCV GT1/HIV-1 coinfection	18/18 (100)	15/15 (100)
SOF-experienced[a] HCV GT1-infected subjects	2/2 (100)	1/1 (100)
Virologic failure, n/N (%) – ITT population		
On-treatment virologic failure	0/352	1/351 (0.3)
$Relapse_{12}$	0/352	0/349

Arm A: ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks

Arm B: ABT-493/ABT-530 300 mg/120 mg QD for 8 weeks

DAA = direct-acting antiviral; GT = genotype; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ITT = intention-to-treat; ITT-MS = all subjects in the ITT population who were HCV monoinfected, including those who were DAA-experienced; LLOQ = lower limit of quantitation; pegIFN = pegylated interferon; QD = once daily; $Relapse_{12}$ = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR_{12} assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment (defined as study drug duration ≥ 77 days for Arm A and ≥ 52 days for Arm B) and had post-treatment data available, excluding reinfection; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR_{12} = sustained virologic response 12 weeks postdosing

a. SOF + RBV ± pegIFN.

Resistance:

The prevalence of baseline polymorphisms at the key subset of amino acid positions in NS3 (at positions 155, 156, or 168) and NS5A (at positions 24, 28, 30, 31, 58, 92, or 93) was: 0.3% (1/343) in NS3 and 27.0% (91/337) in NS5A in GT1-infected subjects in Arm A, and 1.8% (6/335) in NS3 and 27.7% (92/332) in NS5A in GT1-infected subjects in Arm B. The prevalence of polymorphisms at each signature amino acid position in NS3 or NS5A was similar across both arms. The presence of baseline polymorphisms did not impact treatment outcome in subjects infected with HCV GT1 in this study

Pharmacokinetic Results:

The pharmacokinetic exposures of ABT-493 and ABT-530 over 0 – 26 hours after administration of ABT-493/ABT-530 300 mg/120 mg in HCV treatment-naïve or prior treatment-experienced chronic HCV GT1-infected or HCV GT1/HIV-1 coinfected subjects without cirrhosis were comparable in the 12-week and 8-week treatment regimens.

Summary/Conclusions (Continued)

Safety Results:

The percentage of subjects with AEs and with AEs considered related to study drug was comparable between the 12-week (Arm A) and 8-week (Arm B) treatment arms. The majority of subjects experienced at least 1 AE. Most subjects with AEs had events with a maximum severity of Grade 1 (mild) in severity, with the most common overall being headache and fatigue. There was only 1 Grade ≥ 3 AE (Grade 3 asthenia in Arm A) assessed as related to study drug. Nine subjects experienced SAEs, none of which were considered related to study drug. One subject in Arm A prematurely discontinued study drug on Day 78 due to non-study drug-related AEs of dandruff, anxiety, and amnesia. One subject (Arm A) died during the follow-up period due to an AE (preferred term of death; cause of death is unknown), an event considered unrelated to study drug.

No clinically meaningful observations were noted for hematology, clinical chemistry, urinalysis, vital signs, or 12-lead electrocardiogram assessments. There were no subjects with clinically significant alanine aminotransferase elevations. No subjects met criteria for potential hepatotoxicity or experienced an event of hepatic decompensation/hepatic failure.

The nature and frequency of AEs and laboratory abnormalities among HCV GT1/HIV-1 coinfected subjects was similar to that observed in HCV GT1-monoinfected subjects.

Conclusions:

- Treatment of HCV GT1-infected subjects without cirrhosis with 8-week and 12-week regimens of ABT-493/ABT-530 300 mg/120 mg QD achieved high efficacy (SVR_{12} rates > 99%) without relapses. The 12-week regimen was noninferior to the current standard of care (OBV/PTV/r + dasabuvir ± RBV or SOF/LDV for 12 weeks) and the 8-week regimen was noninferior to the 12-week regimen.
- Similarly high efficacy was observed regardless of baseline host or viral factors, including HIV-1 coinfection, fibrosis stage, baseline viral load, prior treatment experience (IFN or pegIFN with or without RBV, or SOF plus RBV with or without pegIFN), HCV GT1 subgenotype, or presence of baseline NS3 and/or NS5A polymorphisms.
- The pharmacokinetic exposures of ABT-493 and ABT-530 over 0 – 26 hours after administration of ABT-493/ABT-530 300 mg/120 mg in HCV treatment-naïve or prior treatment-experienced chronic HCV GT1-infected or HCV GT1/HIV-1 coinfected subjects without cirrhosis were comparable in the 12-week and 8-week treatment regimens.
- The fixed-dose combination of ABT-493/ABT-530 300 mg/120 mg QD demonstrated a favorable safety profile and was well tolerated, with mostly mild AEs. The safety profile of ABT-493/ABT-530 for 8 and 12 weeks was comparable. There were no study drug-related SAEs, no discontinuations due to drug-related AEs, and rare occurrences of clinically significant laboratory abnormalities.
- The optimal treatment duration of ABT-493/ABT-530 in subjects without cirrhosis infected with HCV GT1 (treatment-naïve or -experienced with pegIFN, RBV, or SOF) is 8 weeks; extending treatment duration for an additional 4 weeks does not improve efficacy.