

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: ABT-493 (glecaprevir [GLE])/ABT-530 (pibrentasvir [PIB])	Volume:	
Name of Active Ingredient: GLE: (3 <i>aR</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> ,21 <i>E</i> ,24 <i>aR</i>)-7- <i>tert</i> -butyl- <i>N</i> -{(1 <i>R</i> ,2 <i>R</i>)-2-(difluoromethyl)-1-[(1-methylcyclopropane-1-sulfonyl)carbamoyl]cyclopropyl}-20,20-difluoro-5,8-dioxo-2,3,3 <i>a</i> ,5,6,7,8,11,12,20,23,24 <i>a</i> -dodecahydro-1 <i>H</i> ,10 <i>H</i> -9,12-methanocyclopenta[18,19][1,10,17,3,6]trioxadiazacyclononadecino[11,12- <i>b</i>]quinoxaline-10-carboxamide hydrate PIB: Methyl {(2 <i>S</i> ,3 <i>R</i>)-1-[(2 <i>S</i>)-2-{5-[(2 <i>R</i> ,5 <i>R</i>)-1-{3,5-difluoro-4-[4-(4-fluorophenyl) piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2 <i>S</i>)-1-[<i>N</i> -(methoxycarbonyl)- <i>O</i> -methyl-L-threonyl] pyrrolidin-2-yl}-1 <i>H</i> -benzimidazol-5-yl) pyrrolidin-2-yl]-6-fluoro-1 <i>H</i> -benzimidazol-2-yl} pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl} carbamate.	Page:	
Title of Study: A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Adults with Chronic Hepatitis C Virus (HCV) Genotype 1 – 6 Infection and Human Immunodeficiency Virus-1 (HIV-1) Co-Infection (EXPEDITION-2)		
Coordinating Investigator: [REDACTED]		
Study Sites: 36 sites in Australia, Belarus, France, Germany, Poland, Russian Federation, United Kingdom, and the United States (and its territory, Puerto Rico)		
Publications: 1 abstract		
Studied Period (Years): First Subject First Visit: 17 May 2016 Last Subject Last Visit: 07 June 2017	Phase of Development: 3	

Objectives:

The primary objectives of this study were to compare the sustained virologic response 12 weeks postdosing (SVR₁₂, HCV RNA < lower limit of quantitation [LLOQ] 12 weeks following therapy) of 8 or 12 weeks of treatment with ABT-493 (glecaprevir [GLE])/ABT-530 (pibrentasvir [PIB]) combination in HCV genotype (GT) 1 – 6 infected subjects with HIV-1 coinfection to a predefined threshold, based on the historical SVR₁₂ rate of the current standard of care (i.e., sofosbuvir [SOF]/ledipasvir [LDV] for 12 weeks or grazoprevir [GZV]/elbasvir [ELB] for 12 weeks) and to assess the safety of treatment with the combination regimen GLE/PIB for 8 or 12 weeks in HCV GT1 – 6 infected subjects with HIV-1 coinfection.

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

Methodology:

This was a Phase 3, multicenter, open-label study to evaluate the efficacy and safety of the GLE/PIB combination regimen in HCV treatment-naïve (i.e., subject who had not received a single dose of any approved or investigational anti-HCV medication) or treatment-experienced (i.e., subject who had failed prior interferon (IFN) or pegylated IFN (pegIFN) ± ribavirin (RBV), or SOF + RBV ± pegIFN; excluding GT3 treatment-experienced subjects) adults with chronic HCV GT1 – 6 infection and HIV-1 coinfection with compensated cirrhosis (F4) or without cirrhosis (F0 – F3) for an 8-week (noncirrhotics) or 12-week (cirrhotics) treatment duration. Subjects were required to be naïve to treatment with any HIV-1 antiretroviral treatment (ART) or on a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to screening. The qualifying HIV-1 ART regimen contained one of the following: rilpivirine (RPV), raltegravir (RAL), dolutegravir (DTG), or elvitegravir/cobicistat (EVG/COBI). For noncirrhotic subjects, the qualifying HIV-1 ART regimens could additionally contain one of the following: darunavir (DRV) + ritonavir (r), DRV/COBI, or lopinavir (LPV)/r. In addition, subjects (both cirrhotic and noncirrhotic) could take a nucleoside/nucleotide reverse transcriptase inhibitor (N[t]RTI) backbone containing any of the following: tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), abacavir (ABC), emtricitabine (FTC), or lamivudine (3TC).

Hepatitis C virus GT1 – 6/HIV-1 coinfecting subjects meeting all eligibility criteria were allocated to one of the following treatment arms:

- Arm A: Noncirrhotic subjects treated with GLE/PIB (300 mg/120 mg once daily [QD]) for 8 weeks.
- Arm B: Subjects with compensated cirrhosis treated with GLE/PIB (300 mg/120 mg QD) for 12 weeks.

Safety and efficacy were assessed 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, the emergence and persistence of HCV resistance-associated viral variants, plasma HIV-1 RNA, HIV drug resistance, and assessment of patient-reported outcomes (PROs).

Number of Subjects (Planned and Analyzed):

Planned: approximately 160 subjects

Analyzed: 153 subjects (137 in Arm A and 16 in Arm B) were enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria:

- Male or female (postmenopausal, or permanently surgically sterile, or women of childbearing potential practicing at least 1 protocol-specified method of birth control, starting at Study Day 1 through at least 30 days after the last dose of study drug) at least 18 years of age at time of screening.
- Screening laboratory result indicating HCV GT1, 2, 3, 4, 5, or 6 infection.
- Positive anti-HCV antibody (Ab) and plasma HCV RNA viral load $\geq 1,000$ IU/mL at the Screening Visit.
- Chronic HCV infection, defined as 1 of the following:
 - Positive for anti-HCV Ab or HCV RNA at least 6 months before screening; or
 - A liver biopsy consistent with chronic HCV infection; or
 - Abnormal alanine aminotransferase (ALT) levels for at least 6 months before screening.
- Hepatitis C virus treatment-naïve (has not received a single dose of any approved or investigational anti-HCV medication) or HCV treatment-experienced (has failed prior IFN or pegIFN \pm RBV, or SOF + RBV \pm pegIFN therapy). Genotype 3 subject had to be HCV treatment-naïve.
- Positive test result for anti-HIV Ab at screening.
- Naïve to treatment with any 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 for approximately 30 days after the last dose of study drug, or breastfeeding.
- 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 (HBsAg).
- Hepatitis C virus genotyping performed during screening indicated coinfection with more than 1 HCV genotype.
- Hepatitis C virus genotyping performed during screening indicated HCV GT3 in a subject with prior HCV treatment experience.
- Positive test result at screening for HIV-2 Ab.
- 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 GLE/PIB.
- History of severe, life-threatening, or other significant sensitivity to any excipients of the study drug.

Diagnosis and Main Criteria for Inclusion (Continued):			
Main Exclusion Criteria (Continued):			
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 film-coated tablet/Oral	16-001003
Duration of Treatment:			
Subjects in Arm A received GLE/PIB for 8 weeks.			
Subjects in Arm B received GLE/PIB 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, full length nonstructural viral protein 3/4A (NS3/4A) or nonstructural viral protein 5A (NS5A) from baseline samples were sequenced by next-generation sequencing (NGS). For subjects who experienced virologic failure (on-treatment virologic failure or post-treatment relapse), full length NS3/4A and NS5A genes from first sample after virologic failure with HCV RNA \geq 1000 IU/mL were sequenced by NGS. An appropriate subtype-specific prototypic reference sequence was used for comparison with sequences from samples.			
The following resistance information was analyzed for subjects who received GLE/PIB 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 population or deep 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 sequences, and 3) the persistence of viral resistance by population or deep sequencing.			
If any subject compliant with their ART developed plasma HIV-1 RNA level of \geq 200 copies/mL on first 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:			
Individual plasma concentrations for GLE and PIB were tabulated and summarized.			
Safety:			
Safety and tolerability was assessed by monitoring adverse events (AEs), clinical laboratory tests, vital signs, physical examinations, and 12-lead electrocardiograms.			

Statistical Methods

Efficacy:

The primary efficacy endpoint was SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). The number and percentage of subjects achieving SVR₁₂ were summarized with a 2-sided 95% confidence interval (CI), calculated using the normal approximation to the binomial. If the SVR₁₂ rate was 100%, the Wilson's score method was used to calculate the CI. The percentage of subjects treated with GLE/PIB and achieving SVR₁₂ would be noninferior to the 96% SVR₁₂ rate of the current standard of care (i.e., SOF/LDV for 12 weeks [96%; 321/335] or GZV/ELB for 12 weeks [96%; 210/218]) if the lower confidence bound (LCB) of the 2-sided 95% CI of the percentage of subjects with SVR₁₂ was > 90%.

The secondary efficacy endpoints were:

- The percentage of subjects with on-treatment virologic failure; and
- The percentage of subjects with post-treatment relapse.

The number and percentage of subjects with on-treatment virologic failure and post-treatment relapse was summarized with 2-sided 95% Wilson score CIs.

Resistance:

The genes of interest for NGS in this study in all samples were those encoding full length NS3/4A and NS5A. The following resistance information was analyzed for baseline samples from all subjects:

1) the prevalence of polymorphisms at signature amino acid positions or a key subset of amino acid positions at baseline identified by NGS were compared to the appropriate subtype specific prototypic reference sequence; and 2) comparison of SVR₁₂ rates in subjects with or without baseline polymorphisms was conducted. For subjects experiencing virologic failure, the variants at available postbaseline timepoints identified by NGS were compared with baseline and the appropriate prototypic reference sequences.

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 SVR₁₂ was presented for subgroup variables, such as baseline viral load, prior treatment experience, or HCV GT subtype.

Pharmacokinetic:

Individual plasma concentrations of GLE and PIB were tabulated for each subject. Summary statistics were computed for each sampling time.

Statistical Methods (Continued)

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. 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. 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. The tabulation of the number and percentage of subjects who were on stable ART and had HIV-1 RNA suppression was provided. Mean changes from baseline in lymphocytes (count), and CD8+ and CD4+ T-cell count (absolute and percent) to each postbaseline visit were summarized.

Summary/Conclusions

Efficacy and Resistance Results:

Efficacy:

An overall SVR₁₂ rate of 150/153 (98.0%) with 95% CI of 95.8% to 100.0% was achieved. The primary efficacy endpoint was achieved; efficacy of GLE/PIB based on the intent-to-treat (ITT) population was demonstrated as the 95% LCB for SVR₁₂ was > 90%.

The GLE/PIB regimen demonstrated high efficacy based on a SVR₁₂ rate that was numerically higher than SVR₁₂ rate of 96% for the current standard of care (SOF/LDV or GZV/ELB for 12 weeks).

There was only 1 virologic failure across the overall ITT population: an on-treatment virologic failure in an HCV GT3a-infected HCV treatment-naïve cirrhotic subject. There were no relapses. High efficacy was observed regardless of baseline host or viral factors, including baseline viral load, prior HCV treatment experience, HCV genotype and subtype, and the presence of baseline polymorphisms in NS3 and/or NS5A.

Summary/Conclusions (Continued)	
Efficacy and Resistance Results (Continued):	
<u>Efficacy (Continued):</u>	
Primary Efficacy Endpoint: Virologic Response at Post-Treatment Week 12 (SVR₁₂) (ITT Population)	
Assessment	Overall (N = 153)
SVR ₁₂ , n/N (%)	150/153 (98.0)
95% CI ^a	(95.8, 100.0)
Nonresponders, n/N (%)	3/153 (2.0)
Reasons for nonresponse, n/N (%)	
Virologic failure	1/153 (0.7)
On-treatment virologic failure	1/153 (0.7)
Breakthrough	1/153 (0.7)
EOT failure	0/153
Relapse by post-treatment Week 12	0/151
Non-virologic failure	2/153 (1.3)
Premature study drug discontinuation	1/153 (0.7)
HCV reinfection	0/153
Missing SVR ₁₂ data	1/153 (0.7) ^b
Other	0/153
Threshold based on current standard of care (SOF/LDV for 12 weeks or GZV/ELB for 12 weeks)	
Efficacy threshold	90%
CI = confidence interval; ELB = elbasvir; EOT = end of treatment; GZV = grazoprevir; HCV = hepatitis C virus; ITT = intention-to-treat; LDV = ledipasvir; SOF = sofosbuvir; SVR ₁₂ = sustained virologic response 12 weeks postdosing	
a. Calculated using the normal approximation to the binomial distribution, unless the rate is 100%, in which case the Wilson's score method was used instead.	
b. This Subject [REDACTED] returned for the Post-Treatment Week 24 visit and achieved SVR ₂₄ .	
Note: Backward imputation, where applicable, was used to impute missing data. After applying backward imputation, if there is still no value in the window but there is an HCV RNA value from a local laboratory present, then it will be imputed into the SVR window. Otherwise, subjects with missing data are counted as failures.	
Results for the additional efficacy endpoint for SVR ₂₄ were consistent with the primary efficacy results, with 96.7% agreement between SVR ₁₂ and SVR ₂₄ . One subject relapsed at Post-Treatment Week 24 after achieving SVR ₁₂ .	

Summary/Conclusions (Continued)

Efficacy and Resistance Results (Continued):

Resistance:

Based on phylogenetic analysis of NS3/4A or NS5A sequences from 152 subjects, 2 GT1, 3 GT2, 1 GT3, 2 GT4, and 2 GT6 subtypes were identified in the study, including 66 GT1a-, 21 GT1b-, 1 GT2- (undetermined subtype), 1 GT2a-, 6 GT2b-, 1 GT2c-, 22 GT3a-, 1 GT4a-, 15 GT4d-, and 1 each of GT6e- and GT6n-infected subjects in Arm A; and 5 GT1a-, 5 GT1b-, 1 GT2a-, 4 GT3a-, and 1 GT4a-infected subjects in Arm B.

Baseline polymorphisms at the key subset of amino acid positions in NS3 (at positions 155, 156, or 168) were not detected in GT2- (0/9), GT4- (0/17), or GT6- (0/1) infected subjects, and were detected in 2.1% (2/97) and 3.8% (1/26) of the GT1- and GT3-infected subjects, respectively, at 15% detection threshold. NS5A polymorphisms (at positions 24, 28, 30, 31, 58, 92, or 93) were detected in 19.8% (19/96), 100% (8/8), 24.0% (6/25), 58.8% (10/17), and 50.0% (1/2) of the GT1-, GT2-, GT3-, GT4-, and GT6-infected subjects, respectively, at 15% detection threshold. The prevalence of baseline polymorphisms was similar across Arm A and B. The presence of baseline polymorphisms had no impact on treatment outcome in subjects infected with any HCV subtype in this study in either treatment arm.

One GT3a-infected subject experiencing virologic failure in Arm B had treatment-emergent substitutions Y56H and Q168R in NS3, and S24F and M28K in NS5A at the time of failure. Q168R in NS3 was not detectable at Post-Treatment Week 24, while the other substitutions persisted through this time point.

No subject compliant with their ART met the protocol-defined criterion for HIV drug resistance analysis and, therefore, there are no results for HIV drug resistance testing.

Pharmacokinetic Results:

Plasma concentrations of GLE and PIB over 0 to > 26 hours after administration of multiple GLE/PIB 300 mg/120 mg QD doses were similar in subjects without cirrhosis treated for 8 weeks and in subjects with cirrhosis treated for 12 weeks.

Safety Results:

Approximately 60% of subjects experienced at least 1 AE. Most subjects with AEs had events with a maximum severity of Grade 1 (mild), with the most common overall being fatigue. No subject experienced a study drug-related Grade \geq 3 AE, study drug-related serious adverse event (SAE), or died during the study. Four subjects reported 5 Grade \geq 3 AEs (calculus urinary, cerebral haemorrhage and cerebrovascular accident, peripheral arterial occlusive disease, and upper gastrointestinal haemorrhage); all were SAEs and none were assessed as related to study drug. One subject prematurely discontinued study drug on Day 25 due to non-study drug-related SAEs of cerebrovascular accident and cerebral hemorrhage.

No clinically meaningful observations were noted for hematology, clinical chemistry, urinalysis, vital signs, or 12-lead electrocardiogram assessments. No subject met the criteria for hepatic laboratory abnormalities of special interest and there were no cases consistent with drug-induced liver injury (DILI). No subjects experienced an event of hepatic decompensation/hepatic failure or hepatocellular carcinoma. No case of failure to maintain HIV-1 virologic suppression was identified in subjects compliant with their ART.

Summary/Conclusions (Continued)

Conclusions:

- Treatment of HCV GT1 – GT6/HIV-1 coinfecting subjects with 8-week and 12-week regimens of GLE/PIB 300 mg/120 mg QD in noncirrhotics and cirrhotics, respectively, achieved overall SVR₁₂ rate of 98.0% without relapses. The efficacy of GLE/PIB regimen based on the high SVR₁₂ rate was numerically higher than the current standard of care (SOF/LDV or GZV/ELB for 12 weeks).
- Similarly high efficacy was observed regardless of baseline host or viral factors, including baseline viral load, prior treatment experience (IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN), HCV genotype and subtype, and presence of baseline NS3 and/or NS5A polymorphisms.
- SVR₂₄ rates were consistent with the primary efficacy results, with 96.7% agreement between SVR₁₂ and SVR₂₄. One subject relapsed at Post-Treatment Week 24 after achieving SVR₁₂.
- Plasma concentrations of GLE and PIB over 0 to > 26 hours after administration of multiple GLE/PIB 300 mg/120 mg QD doses were similar in subjects without cirrhosis treated for 8 weeks and in subjects with compensated cirrhosis treated for 12 weeks.
- The fixed-dose combination of GLE/PIB 300 mg/120 mg QD demonstrated a favorable safety profile and was well tolerated, with mostly mild AEs. There were no study drug-related SAEs, no discontinuations due to drug-related AEs, and infrequent occurrences of significant laboratory abnormalities.
- The optimal treatment duration of GLE/PIB in subjects coinfecting with HCV GT1 – GT6/ HIV-1 (treatment-naïve or -experienced with pegIFN, RBV, or SOF [with the exception of GT3 treatment experienced]) is 8 weeks for noncirrhotics and 12 weeks for cirrhotics.