

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: Page:	
Name of Active Ingredient: GLE: (3a <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> ,21 <i>E</i> ,24a <i>R</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-2,3,3a,5,6,7,8,11,12,20,23,24a-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		
Title of Study: A Single-Arm, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of ABT-493/ABT-530 in Adult Post-Liver or Post-Renal Transplant Recipients with Chronic Hepatitis C Virus Genotype 1 – 6 Infection (MAGELLAN-2)		
Coordinating Investigator: ████████████████████		
Study Sites: 27 sites in Australia, Canada, Italy, New Zealand, Spain, Taiwan, United Kingdom, and the United States (and its territory, Puerto Rico)		
Publications: 1 abstract		
Studied Period (Years): First Subject First Visit: 22 April 2016 Last Subject Last Visit: 29 June 2017	Phase of Development: 3	

Objectives:

The primary objectives of this study were to compare the 12-week sustained virologic response, SVR₁₂ (hepatitis C virus [HCV] RNA < lower limit of quantitation [LLOQ] 12 weeks following therapy) of 12 weeks of treatment with the ABT-493 (glecaprevir [GLE])/ABT-530 (pibrentasvir [PIB]) combination regimen in adults with HCV genotype (GT) 1 – 6 infection who were post-primary orthotopic liver transplant or renal transplant to a predefined threshold, based on the historical SVR₁₂ rate for the current standard of care regimens (sofosbuvir [SOF]/ledipasvir [LDV] + ribavirin [RBV] or SOF + daclatasvir [DCV] + RBV) and to assess the safety of treatment with the GLE/PIB combination regimen for 12 weeks in adults with HCV genotype GT1 – 6 infection and post-primary orthotopic liver transplant or renal transplant.

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

Methodology:

This was a Phase 3, single-arm, open-label, multicenter study to evaluate the safety and efficacy of GLE/PIB in chronic HCV GT1 – 6 infected, post-primary orthotopic liver or renal transplant subjects without cirrhosis (F0 – F3) who were either HCV treatment-naïve or prior treatment-experienced with interferon (IFN) or pegylated interferon (pegIFN) with or without RBV or SOF with RBV with or without pegIFN (except GT3-infected subjects who must have been treatment-naïve).

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, 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 90 subjects.

Analyzed: 100 subjects 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.

Diagnosis and Main Criteria for Inclusion (Continued):

Main Inclusion Criteria (Continued):

- Hepatitis C virus treatment-naïve (had not received a single dose of any approved or investigational anti-HCV medication) or HCV treatment experienced (had failed prior IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN therapy), pre- or post-transplant. Previous HCV treatment had to be completed ≥ 2 months prior to screening. Genotype 3 subject had to be HCV treatment-naïve.
- Recipient of a cadaveric or living donor liver transplant which was a consequence of HCV infection ≥ 3 months prior to screening or received a cadaveric or living donor kidney at least ≥ 3 months before screening.
- Documented as noncirrhotic.
- Subject was on a stable immunosuppression regimen based on tacrolimus, sirolimus, everolimus, mycophenolate mofetil, mycophenolic acid, azathioprine and/or cyclosporine.

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 or anti-human immunodeficiency virus (HIV) Ab.
- Hepatitis C virus genotyping performed during screening indicated coinfection with more than 1 HCV genotype or HCV genotype was indeterminate.
- Any cause of liver disease post-transplantation other than chronic HCV infection.
- Clinical history of fibrosing cholestatic hepatitis post-transplant.
- Re-transplantation of the liver or kidney.
- Steroid resistant rejection of the transplanted liver or kidney, or a history of rejection treated with high dose steroid within 3 months of screening.
- History of post-transplant complications related to hepatic or renal vasculature.
- 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.

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
ABT-493/ABT-530 = glecaprevir (GLE)/pibrentasvir (PIB)			

Duration of Treatment:

Subjects received GLE/PIB 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 GLE/PIB, the variants 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 analyzed for subjects who received GLE/PIB who did not achieve SVR₁₂ and who had a postbaseline sample with HCV RNA \geq 1000 IU/mL: 1) the 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 sequence, and 3) the persistence of viral resistance by population or deep sequencing.

Pharmacokinetic:

Individual plasma concentrations for GLE and PIB were tabulated and summarized. Individual daily doses of the immunosuppressants cyclosporine, sirolimus, everolimus, and/or tacrolimus were also 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 in the ITT population achieving SVR₁₂ were summarized with a 2-sided 95% confidence interval, calculated using the normal approximation to the binomial distribution. If the SVR₁₂ rate was 100%, the Wilson's score method was used to calculate the confidence interval. The lower confidence bound (LCB) of the 2-sided 95% confidence interval (CI) for the percentage of subjects achieving SVR₁₂ must have exceeded 86% to achieve noninferiority to the standard of care (i.e., SOF/LDV + RBV or SOF + DCV + RBV for 12 weeks).

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 post-treatment 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 with HCV RNA $<$ LLOQ at the end of treatment; subjects with reinfection were summarized separately).

Statistical Methods (Continued)

Efficacy (Continued):

For the analysis of relapse, completion of treatment was defined as any subject with study drug duration of 77 days or greater. The number and percentage of subjects was summarized along with 2-sided 95% Wilson score confidence intervals.

Resistance:

The genes of interest for next-generation sequencing (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 variants at signature amino acid position at baseline identified by NGS were compared to the appropriate prototypic reference sequence; and 2) comparison of SVR₁₂ rates in subjects with or without baseline variants was conducted. For subjects not achieving SVR₁₂ or SVR₂₄, sequences at available postbaseline timepoints were compared to baseline and appropriate prototypic reference sequences to identify treatment-emergent substitutions.

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 were calculated, along with the corresponding 2-sided 95% Wilson score CIs, for subgroup variables such as HCV genotype and available subtype, prior HCV treatment history, organ transplant type, interleukin 28B genotype, and baseline HCV RNA level.

Pharmacokinetic:

Individual plasma concentrations of GLE and PIB 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 GLE and PIB for visits at or after Week 1 were summarized. Daily doses of cyclosporine, tacrolimus, everolimus, and sirolimus were tabulated prior to dosing and on Days 7, 28, 56, and 84.

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.

Summary/Conclusions

Efficacy Results:

An overall SVR₁₂ rate of 98/100 (98.0%) with 95% CI of 95.3% to 100.0% was observed. The primary efficacy endpoint was achieved; efficacy of GLE/PIB based on ITT population was demonstrated as the 95% LCB for SVR₁₂ was > 86%.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

The GLE/PIB regimen demonstrated high efficacy based on an SVR₁₂ rate that was numerically higher than the SVR₁₂ rate of 94% for the current standard of care (SOF/LDV + RBV or SOF + DCV + RBV for 12 weeks).

No subject experienced on-treatment virologic failure and 1 subject (1.0%) experienced post-treatment relapse by Post-Treatment Week 4. High efficacy was observed regardless of baseline host or viral factors, including baseline viral load, prior HCV treatment history, HCV genotype and subtype, transplant organ type, immunosuppressant medication type, or the presence of baseline polymorphisms in NS3 and/or NS5A.

Primary Efficacy Endpoint: Sustained Virologic Response 12 Weeks Post-Treatment (SVR₁₂) (ITT Population)

Assessment	Overall N = 100
SVR ₁₂ , n/N (%)	98/100 (98.0)
95% CI ^a	(95.3, 100.0)
Nonresponders, n/N (%)	2/100 (2.0)
Reasons for nonresponse, n/N (%)	
Virologic failure	1/100 (1.0)
On-treatment virologic failure	0/100
Breakthrough	0/100
EOT failure	0/100
Relapse by Post-Treatment Week 12	1/99 (1.0)
Non-virologic failure	1/100 (1.0)
Premature study drug discontinuation	0/100
HCV reinfection	0/100
Missing SVR ₁₂ data	1/100 (1.0)
Other	0/100
Threshold based on current standard of care (SOF/LDV + RBV or SOF + DCV + RBV for 12 weeks)	
Efficacy threshold	86% ^b

CI = confidence interval; DCV = daclatasvir; EOT = end of treatment; HCV = hepatitis C virus; ITT = intention-to-treat; LDV = ledipasvir; RBV = ribavirin; SOF = sofosbuvir; SVR₁₂ = 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. Established by applying an 8% noninferiority margin to the historical SVR₁₂ rate of 94%.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

The SVR₂₄ rate was consistent with the primary efficacy result, with 96.0% agreement between SVR₁₂ and SVR₂₄. One subject relapsed at Post-Treatment Week 24 after achieving SVR₁₂.

Resistance Results:

Based on phylogenetic analysis of NS3/4A or NS5A sequences from 99 subjects, 2 GT1, 4 GT2, 1 GT3, 3 GT4, and 1 GT6 subtypes were identified in the study, including 27 GT1a-, 29 GT1b-, 2 GT2a-, 9 GT2b-, 1 GT2c-, 1 GT2i-, 24 GT3a-, 1 GT4a-, 2 GT4d-, 1 GT4r-, and 2 GT6a-infected subjects.

Baseline polymorphisms at the key subset of amino acid positions in NS3 (at positions 155, 156, or 168) were not detected in any HCV genotype. NS5A baseline polymorphisms (at positions 24, 28, 30, 31, 58, 92, or 93) were detected in 19.6% (11/56), 83.3% (10/12), 20.8% (5/24), 100% (4/4), and 100% (2/2) of the GT1-, GT2-, GT3-, GT4-, and GT6-infected subjects, respectively, at 15% detection threshold. The presence of baseline polymorphisms had no impact on treatment outcome in GT1-, GT2-, GT4-, or GT6-infected subjects. Baseline polymorphisms in NS3 were not associated with virologic failure in GT3-infected subjects. In NS5A, 1 of 3 GT3-infected subjects with baseline Y93H experienced virologic failure. Given the small number of GT3-infected subjects with Y93H in NS5A, it is unclear whether baseline Y93H has an impact on treatment outcome.

The GT3a-infected subject experiencing virologic failure at Post-Treatment Week 4 did not have baseline polymorphisms in NS3 and had treatment-emergent substitution Y56H in NS3 at the time of failure. Y93H in NS5A was detected at baseline and at the time of failure in this subject. NS3 Y56H was not detectable, while NS5A Y93H remained detectable at Post-Treatment Week 24.

One GT3a-infected subject experiencing virologic failure at Post-Treatment Week 24 had no baseline polymorphisms or treatment-emergent substitutions in NS3 or NS5A, is a suspected intravenous drug user, and achieved SVR₁₂.

Pharmacokinetic Results:

Plasma concentrations of GLE and PIB after administration of multiple GLE/PIB 300 mg/120 mg QD doses were summarized. Median total daily doses of cyclosporine, everolimus, and sirolimus were unchanged throughout the duration of the study. Median total daily tacrolimus dose slightly decreased from baseline to Day 7, but remained unchanged throughout the remainder of the study.

Summary/Conclusions (Continued)

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), with the most common overall being fatigue, headache, nausea, pruritus, and diarrhea. Two subjects, both liver transplant recipients, experienced Grade ≥ 3 AEs (Grade 3 hepatic enzyme increased and sinusitis in 1 subject each) assessed as related to study drug; the event of sinusitis was serious. There were no DAA-related SAEs in the renal transplant population. One subject experienced SAEs of cerebrovascular accident and arteriovenous malformation on Day 50 which led to premature discontinuation of study drug (last dose of study drug was on Day 49); the events were considered not related to 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. No cases of drug-induced liver injury, hepatic decompensation, or hepatocellular carcinoma were identified. One case of mild liver transplant rejection occurred while the subject was taking GLE/PIB, which was managed with titration of immunosuppression regimen, without changes in GLE/PIB dosing.

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

Conclusions:

- Treatment of HCV GT1 – 6-infected, post-primary orthotopic liver or renal transplant subjects without cirrhosis with a 12-week regimen of GLE/PIB 300 mg/120 mg QD achieved high efficacy (overall SVR₁₂ rate 98.0%). The efficacy of the GLE/PIB regimen was demonstrated based on the high SVR₁₂ rate that was numerically higher than the current standard of care (SOF/LDV + RBV or SOF + DCV + RBV for 12 weeks).
- A low relapse rate (2%) was observed.
- High efficacy was observed regardless of baseline host or viral factors, including baseline viral load, prior HCV treatment history, HCV genotype and subtype, transplant organ type, immunosuppressant medication type, or the presence of baseline polymorphisms in NS3 and/or NS5A.
- The SVR₂₄ rate was consistent with the primary efficacy result, with 96.0% agreement between SVR₁₂ and SVR₂₄.
- The fixed-dose combination of GLE/PIB 300 mg/120 mg QD for 12 weeks was well tolerated and demonstrated a favorable safety profile.