

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: ABT-450, ritonavir, ABT-267, ABT-333, ribavirin	Volume:	
Name of Active Ingredient: ABT-450: (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-[[[(5-methylpyrazin-2-yl)carbonyl]amino]-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate ritonavir: [5S-(5R*,8R*,10R*,11R*)]10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester ABT-267: Dimethyl ([[2S,5S)-1-(4-tert-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diyl}carbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]])biscarbamate hydrate ABT-333: (sodium N-{6-[3-tert-butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl]naphthalen-2-yl}methanesulfonamide hydrate) Ribavirin: 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide	Page:	
Title of Study: Open-Label, Phase 2 Study to Evaluate the Safety and Efficacy of the Combination of ABT-450/Ritonavir/ABT-267 With ABT-333 and With or Without RBV in HCV Genotype 1 and ABT-450/r/ABT-267 with RBV in HCV GT4-Infected Adult Liver or Renal Transplant Recipients With Hepatitis C Virus (HCV) Infection (CORAL-I)		
Coordinating Investigator: ██████████		
Study Sites: 18 investigative sites in Australia, the European Union, and the United States.		
Publications: 7 manuscripts and 2 abstracts		

<p>Studied Period (Years): First Subject First Visit: 25 February 2013 Last Subject Last Visit: 13 July 2017</p>	<p>Phase of Development: 2</p>
<p>Objectives: The primary objectives of this study were to assess safety and efficacy (the percentage of subjects achieving a 12-week sustained virologic response (SVR₁₂) [HCV RNA < lower limit of quantification {LLOQ} 12 weeks following treatment]) of coformulated Paritaprevir/Ritanovir and Ombitasvir (OBV/PTV/r) and Dasabuvir (DSV) and with or without Ribavirin (RBV) in HCV genotype (GT)1-infected adult liver or renal transplant recipients and OBV/PTV/r with RBV in HCV GT4-infected adult liver transplant recipients. The secondary objectives of this study were to assess the percentage of subjects with SVR₂₄ (HCV RNA < LLOQ 24 weeks after the last actual dose of study drugs), the percentage of subjects with virologic failure during treatment, and the percentage of subjects with relapse post-treatment.</p>	
<p>Methodology: This was a Phase 2, open-label, multicenter study evaluating the safety and efficacy of OBV/PTV/r with DSV and with or without RBV in HCV GT1-infected adult liver or renal transplant recipients. This study also evaluated the safety and efficacy of OBV/PTV/r with RBV in GT4-infected adult liver transplant recipients. The study design included six cohorts of subjects:</p> <p>Cohort 1 Arm A: OBV/PTV/r 25 mg/150 mg/100 mg once daily (QD) + DSV 250 mg twice daily (BID) + RBV for 24 weeks</p> <p>Cohort 2 Arm B: OBV/PTV/r 25 mg/150 mg/100 mg QD + DSV 250 mg BID + RBV for 24 weeks Arm C: OBV/PTV/r 25 mg/150 mg/100 mg QD + DSV 250 mg BID for 24 weeks</p> <p>Cohort 3 Arm D: OBV/PTV/r 25 mg/150 mg/100 mg QD + DSV 250 mg BID + RBV for 24 weeks Arm E: OBV/PTV/r 25 mg/150 mg/100 mg QD + DSV 250 mg BID + RBV for 12 weeks</p> <p>Cohort 4 Arm F: OBV/PTV/r 25 mg/150 mg/100 mg QD + DSV 250 mg BID + RBV for 12 weeks Arm G: OBV/PTV/r 25 mg/150 mg/100 mg QD + DSV 250 mg BID for 12 weeks</p> <p>Cohort 5 Arm H: OBV/PTV/r 25 mg/150 mg/100 mg QD + DSV 250 mg BID + RBV for 12 weeks Arm I: OBV/PTV/r 25 mg/150 mg/100 mg QD + DSV 250 mg BID for 12 weeks</p> <p>Cohort 6 Arm J: OBV/PTV/r 25 mg/150 mg/100 mg QD + RBV for 12 weeks Arm K: OBV/PTV/r 25 mg/150 mg/100 mg QD + RBV for 24 weeks Within Cohorts 2 – 5, treatment assignment was based on prior HCV treatment experience (if subgenotype 1b, Cohort 2 only) and HCV subgenotype. Within Cohort 6, treatment assignment was based on presence/absence of cirrhosis.</p>	

Methodology (Continued):

For Cohort 1, approximately 30 HCV GT1-infected treatment-naïve or treatment-experienced (conventional interferon or pegylated interferon with or without RBV prior to transplant) liver transplant recipients were to be enrolled in this trial. Cohort 2 was originally designed to enroll 40 HCV GT1a- or GT1b-infected subjects. HCV GT1b-infected subjects who were treatment-naïve or who received prior Interferon (IFN) therapy (post-transplant) and were treatment responders were enrolled and assigned to Study Arm C. Cohorts 3, 4, and 5 were originally designed to enroll 105 HCV GT1-infected subjects representing three subpopulations of subjects: liver transplant recipients with Child Pugh A cirrhosis (Cohort 3, N = 40), liver transplant recipients who are > 3 months post-transplant without cirrhosis (Cohort 4, N = 40), and renal transplant recipients with fibrosis \leq F3 by Metavir scale (or equivalent score by a different scoring system) (Cohort 5, N = 25). Cohort 6 was originally designed to enroll up to 20 liver transplant recipients who were > 3 months (> 91 days) post-transplant with HCV GT4-infection. Subjects were enrolled into the study for a total of 72 weeks, not including a 35-day Screening Period and a Study Treatment Lead-In Period up to 14 days prior to enrollment into the study. This study consisted of 2 periods, the Treatment Period and the Post-Treatment Period.

After the Screening Period, subjects who met the eligibility criteria entered the Study Treatment Lead-In Period, which occurred up to 14 days but no less than 2 days prior to enrollment into the Treatment Period. During the Study Treatment Lead-In Period, subjects who met enrollment criteria returned to the site for laboratory tests to measure the calcineurin inhibitor (CNI) trough level. This trough level served to confirm that the CNI dose was appropriate before commencing study drugs and formed the basis for CNI dose adjustment when the subject commenced the direct-acting antiviral agent (DAA)-RBV therapy. During the Treatment Period, patients received 24 weeks of OBV/PTV/r, DSV, and RBV.

Visits occurred during the Treatment Period at Day 1, 3, 7, 10 (optional), and Weeks 2, 3, 4, 6, 8, 12, 16, 20, and 24. During the Post-Treatment Period, visits occurred at Day 3, 7, 10 (optional), and Weeks 2, 3, 4, 8, 12, 24, 36, and 48.

The safety data were reviewed by AbbVie, as this was an open-label study, and by an independent Data Monitoring Committee during the Treatment Period of the study. There were no findings that required modification or discontinuation of the study.

The following criteria were considered evidence of virologic failure while the subject was on study drugs and these subjects were discontinued from DAA therapy:

- confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of $> 1 \log_{10}$ International Units Per Millilitre [IU/mL] above nadir) at any time point during treatment,
- failure to achieve HCV RNA $<$ LLOQ by Week 6; or
- confirmed HCV RNA \geq LLOQ (defined as 2 consecutive HCV RNA measurements \geq LLOQ) at any point during treatment after HCV RNA $<$ LLOQ.

All subjects who received at least 1 dose of DAAs were monitored for up to 48 weeks following the last dose of DAA for the durability of viral response, safety, and for the emergence and persistence of resistant viral variants in the Post-Treatment Period.

Number of Subjects (Planned and Analyzed):

Planned: up to 195 subjects (approximately 30 subjects in Cohort 1, approximately 40 subjects in Cohort 2, approximately 40 subjects in Cohort 3, approximately 40 subjects in Cohort 4, approximately 25 subjects in Cohort 5, and approximately 20 subjects in Cohort 6).

Analyzed: 129 subjects (34 subjects in Cohort 1, 40 subjects in Cohort 2, 6 subjects in Cohort 3, 34 subjects in Cohort 4, 12 subjects in Cohort 5, and 3 subjects in Cohort 6).

Diagnosis and Main Criteria for Inclusion:

Male or female subjects (18 to 70 years of age, inclusive, at the time of enrollment) who had received liver or renal transplantation as a consequence of HCV GT1 or 4 infection no less than 12 months before the Screening Visit. Subjects must have had a liver biopsy which showed evidence of fibrosis \leq F2 (Metavir scale) and which was obtained within the 6 months prior to the screening period but not less than 9 months post-transplant or during the Screening Period. Subjects must have been currently taking an immunosuppressant regimen based on either tacrolimus or cyclosporine where doses of immunosuppressant drugs had not been increased over the 2 months prior to screening and no new drugs had been added for at least 2 months before screening. Corticosteroids such as prednisone or prednisolone were permitted as components of the immunosuppressant regimen providing the dose was not more than 5 mg/day.

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

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
OBV/PTV/r	AbbVie ^a	Oral	Tablet	75 mg/50 mg/ 12.5 mg	12-006474 12-008149 13-005537 14-002317
DSV	AbbVie ^a	Oral	Tablet	250 mg	12-003057 13-000242 14-002089 14-005074
RBV	Roche or generic manufacturer	Oral	Tablet	200 mg	12-005354, 12-004860 12-005991 14-001228 13-001406 13-005318 15-004138

a. Abbott Laboratories at time of production.

Duration of Treatment:

Subjects received OBV/PTV/r and DSV coadministered with or without RBV for 12 or 24 weeks.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:
Not applicable.

Criteria for Evaluation

Efficacy:

Plasma HCV RNA (IU/mL) was assessed at each Treatment and Post-Treatment Visit.

Resistance:

The following resistance information was tabulated and summarized for subjects who experienced virologic failure: the variants at each amino acid position at baseline identified by population nucleotide sequencing were compared to the appropriate prototypic reference sequence and the variants at the available postbaseline time points identified by population and/or clonal nucleotide sequencing were compared to baseline and the appropriate prototypic reference sequences.

Patient-Reported Outcomes:

The change in non-disease specific health-related quality-of-Life (HRQoL), HCV-specific function and wellbeing, and Health State Utility were assessed using the Short-Form 36 Version 2 health survey (SF-36v2), the HCV Patient Reported Outcomes Instrument (HCV-PRO), and the EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L), including the integral visual analogue scale (VAS), respectively.

Pharmacokinetic:

Plasma concentrations of PTV, OBV, DSV, DSV M1 metabolite, ritonavir, and RBV were tabulated for each subject and group. Blood concentrations of cyclosporine and tacrolimus were tabulated for each subject and group. Summary statistics were computed for each time and visit.

Safety:

Safety and tolerability was assessed by monitoring adverse events, physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECGs), and vital signs.

Statistical Methods

Efficacy:

The primary endpoint was the percentage of subjects with SVR₁₂. The secondary objectives of this study were to assess the percentage of subjects with SVR₂₄, the percentage of subjects with virologic failure during treatment, and the percentage of subjects with relapse post-treatment. For the primary and secondary endpoints, the simple percentage of subjects meeting the endpoint was calculated and a 2-sided 95% confidence interval using the Wilson score method for the binomial proportion was computed.

Resistance:

For all subjects receiving study drug, the variants at each amino acid position at baseline identified by population nucleotide sequencing were compared to the appropriate prototypic reference sequence. For subjects who experienced virologic failure, the variants at available post-baseline time points identified by population and/or next-generation sequencing were compared to baseline and the appropriate prototypic reference standard sequences. The persistence of treatment-emergent substitutions through Post-Treatment Week 48 was summarized.

Statistical Methods (Continued)

Patient-Reported Outcomes:

Exploratory analyses of the change in non-disease-specific HRQoL, HCV-specific function and wellbeing, and health state utility were measured using the SF-36v2, HCV-PRO, and EQ-5D-5L instruments, respectively. SF-36v2 and HCV-PRO were analyzed by their total/component scores, as appropriate. The EQ-5D-5L was analyzed by utility score and by VAS response. Change from baseline in the patient-reported outcome summary measures was assessed.

Pharmacokinetic:

Individual plasma concentrations of PTV, OBV, DSV, DSV M1 metabolite, ritonavir, and RBV were tabulated and summarized by coadministered drug group (tacrolimus or cyclosporine) and study cohort, and cirrhosis status. Individual blood concentrations of cyclosporine and tacrolimus were tabulated and summarized for central and local laboratories, respectively, and by study cohort and cirrhosis status. Summary statistics were computed for each time and visit.

Safety:

The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Tabulations were also provided in which the number of subjects reporting an adverse event (MedDRA preferred term) was presented by severity (mild, moderate, or severe) and relationship to study drugs. Change from baseline in laboratory tests and vital sign measurements to each time point of collection was summarized. Laboratory test and vital sign values that were potentially clinically significant (PCS), according to predefined criteria, were identified and the number and percentage of subjects with PCS values were calculated.

Summary/Conclusions

Efficacy Results:

SVR₁₂ rates ranged from 95.5 – 100% for all Arms, except renal transplant patients in Arm H. The SVR₁₂ rate for Arm H was 66.7 % (6/9). No subjects in Arm H experienced virologic failure, however, 2 subjects from Arm H prematurely discontinued study drug due to AEs and did not achieve SVR₁₂. One subject experienced on-treatment virologic failure (Arm B) and 2 subjects experienced relapse by Post-treatment Week 12 (Arm A and Arm F).

Resistance Results:

Baseline NS3 polymorphisms were predominant at amino acid position 80 in GT1a and 56 in GT1b; overall, baseline NS3 polymorphisms were detected in 40.5% (32/79) and 22.5% (9/40) of the GT1a- and GT1b-infected subjects, respectively. Baseline NS5A polymorphisms at signature amino acid positions were detected in 24.7% (20/81) and 60.0% (24/40) of the GT1a- and GT1b-infected subjects, respectively. Baseline NS5B polymorphisms, predominantly at amino acid positions 316 or 556, were detected in 8.5% (7/82) and 31.7% (13/41) of the GT1a- and GT1b-infected subjects, respectively. The 3 GT4-infected subjects in Cohort 6 did not have baseline polymorphisms in NS3, but all 3 had polymorphisms at position 58 in NS5A. Baseline polymorphisms in NS3, NS5A, or NS5B had no impact on treatment outcome.

Summary/Conclusions (Continued)

Resistance Results (Continued):

Among the 3 GT1a-infected subjects (1 each in Arms A, B, and F) experiencing virologic failure, NS3 V55I/Q80K or Q80K were each detected in 1 subject at baseline; treatment-emergent substitutions R155K, Y56H/D168A, or D168V were each detected in 1 subject. NS3 D168V was detectable through post-treatment Week 24 in 1 subject, and R155K or Y56H/D168A each persisted in 1 subject through post-treatment Week 48. NS5A Q30R was detected in 1 subject at baseline and at the time of failure, and M28T/Q30R or Q30R each emerged at the time of failure in 1 subject. NS5A M28T or Q30R persisted through post-treatment Week 48. Baseline NS5B polymorphisms were not detected in the 3 subjects and treatment emergent C451R/G558R or G554S were each detected in 1 subject; these substitutions did not persist through Post-Treatment Week 24.

Patient-Reported Outcomes Results:

For more than half of subjects decreases in SF-36v2 Mental Component Summary and Physical Component Summary scores did not meet criteria to be considered even of minimal importance. Improvements from baseline mean were observed at Post-Treatment Week 12 for EQ-5D-5L VAS score and HCV-PRO total score, while a small change from baseline mean was observed for EQ-5D-5L health index score.

Pharmacokinetic Results:

For each DAA and RBV, the range of trough plasma concentration (C_{trough}) values overlapped among subjects on tacrolimus and on cyclosporine.

Following the recommended reduction in dose/dosing frequency of cyclosporine (one fifth of the pre-DAA treatment dose administered QD, with subsequent modifications in cyclosporine dose guided by the scheduled cyclosporine trough level testing) or tacrolimus (initial recommended dose of 0.5 mg to be administered every 7 days or 0.2 mg to be administered every 72 hours, with subsequent dose and dosing frequency modifications in tacrolimus made based on the individual drug level data) when administered with DAAs, the geometric mean and range of cyclosporine or tacrolimus blood concentrations during the DAA Treatment Period were comparable to those observed in the Lead-In Period.

Safety Results:

The safety population included all subjects who received at least 1 dose of study drug (N = 129).

The most common treatment-emergent adverse events (TEAEs) were fatigue, headache, nausea, anemia, and diarrhea. Treatment-emergent adverse events were mild or moderate in severity for the majority of subjects.

Summary/Conclusions (Continued)

Safety Results (Continued):

In Cohort 1, two (5.9%) subjects experienced treatment-emergent serious adverse events (hypotension and tachycardia in 1 subject and edema peripheral and pain in extremity in 1 subject). The events of hypotension and tachycardia were considered by the investigator to have a reasonable possibility of being related to DAA treatment. One (2.9%) subject discontinued study drug due to TEAEs of memory impairment, anxiety, and rash; all 3 events were considered by the investigator to be moderate in severity and to have a reasonable possibility of being related to study drug. These events resolved with discontinuation of study drug and the subject achieved SVR₁₂. In Cohort 4, one subject experienced acute kidney injury, which was considered by the investigator to be severe and have a reasonable possibility of being related to DAA treatment, but not RBV. In Cohort 5, 3 subjects experienced a TEAE that was considered by the investigator to be severe and had a reasonable possibility of being related to study drug. One subject experienced a fatal overdose of tacrolimus and 1 subject experienced atypical pneumonia and acute respiratory failure. Study drugs were discontinued and the event of atypical pneumonia was considered ongoing at the end of the study. This subject also experienced acute kidney injury, but that was considered by the investigator to have no reasonable possibility of being related to study drug. One subject experienced severe nausea and vomiting and presented to the emergency room. The subject withdrew consent from the study and symptoms resolved by Day 7.

The majority of subjects with hemoglobin levels < lower limit of normal (LLN) had reductions to Grade 1 or Grade 2. Four subjects experienced a Grade 3 hemoglobin value; no subjects experienced a Grade 4 value.

The number of subjects with postbaseline aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels of at least Grade 2 were low. No subject had a postbaseline Grade 3 AST, 1 subject had a postbaseline Grade 3 alkaline phosphatase level. Four subjects experienced a Grade 3 ALT measurement. For 1 subject from Cohort 1 the Grade 3 ALT occurred at Day 3 which had declined from Day 1 and then declined further with ongoing treatment.

Two (5.9%) subjects in Cohort 1, one (2.5%) in Cohort 2, four (11.8%) subjects in Cohort 4, and 1 (8.3%) subject in Cohort 5 had a postbaseline bilirubin level of Grade 3. No subject experienced a Grade 4 bilirubin level. One of these subjects experienced an AE of jaundice related to having a Grade 3 bilirubin value. None of these subjects experienced AEs of ocular icterus, or yellow skin. One subject had ALT and total bilirubin values that met biochemical criteria for inclusion in Hy's law quadrant; however, this subject did not have clinical evidence of drug-induced liver injury, and the elevated bilirubin level preceded the elevated ALT level.

Summary/Conclusions (Continued)

Safety Results (Continued):

CNI levels were monitored closely throughout the study by means of postdose testing to inform the scheduling of the next dose. Six subjects in Cohort 2 and 1 subject in Cohort 5 had a cyclosporine postdose level > 225.0 ng/mL. Tacrolimus posedose levels > 15.0 ng/mL were identified in 7 subjects in Cohort 1, 1 subject each in Cohorts 2 and 3, 8 subjects in Cohort 4, and 3 subjects in Cohort 5. For Cohort 1, in 2 subjects the elevated tacrolimus levels occurred in the PTP. Of these 7 subjects in Cohort 1 with elevated tacrolimus levels, 2 had creatinine levels that met PCS criteria and resolved during follow-up. In Cohorts 2 and 3, none of the subjects with elevated tacrolimus levels met PCS criteria for creatinine elevation. In Cohort 4, 1 of the 8 subjects with elevated tacrolimus levels met PCS criteria for creatinine elevation. In Cohort 5, 2 of the 3 subjects with elevated tacrolimus levels met PCS criteria for creatinine elevation; A total of 16 subjects had 1 or more postdose tacrolimus levels below the laboratory's reference range of < 2.0 ng/mL or < 1.5 ng/mL. All occurrences except 3, occurred after completion of study drug through Post-Treatment Week 2. None of these subjects had a reported AE of rejection.

No clinically meaningful results of urinalysis, vital signs, or ECG were observed.

Conclusions:

In post-liver transplant HCV GT1-infected adults without cirrhosis, a 12- or 24-week regimen of OBV/PTV/r and DSV plus RBV achieved a high SVR₁₂ rate, with a low rate of on-treatment virologic failure or relapse. It is not possible to draw similar conclusions for GT1-infected cirrhotic patients post liver transplant, GT1-infected adults post renal transplant, or GT4-infected adults post liver transplant because of small numbers of patients enrolled or completing therapy in these populations; however the overall virologic responses observed in these small cohorts are consistent with those seen in the other study cohorts. OBV/PTV/r and DSV with or without RBV was generally well tolerated, with 5 subjects discontinuing study drug because of TEAEs. Adverse events reported in this study were generally consistent with the established safety profile for RBV and those demonstrated for the combination of these 3-DAA's with or without RBV in previous studies. However, due to the significant interactions between OBV/PTV/r and both cyclosporine and tacrolimus, reduction of the immunosuppressant dose and close monitoring of plasma levels during co-administration and at the end of DAA therapy are necessary.