

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-267: Dimethyl ([[(2 <i>S</i> ,5 <i>S</i>)-1-(4- <i>tert</i> -butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2 <i>S</i>)pyrrolidine-2,1-diyl}[(2 <i>S</i>)-3-methyl-1-oxobutane-1,2-diyl]])biscarbamate hydrate ABT-450: (2 <i>R</i> ,6 <i>S</i> ,12 <i>Z</i> ,13 <i>aS</i> ,14 <i>aR</i> ,16 <i>aS</i>)- <i>N</i> -(cyclopropylsulfonyl)-6-[[[(5-methylpyrazin-2-yl)carbonyl]amino]-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13 <i>a</i> ,14,15,16,16 <i>a</i> -tetradecahydrocyclopropa[e]pyrrolo[1,2- <i>a</i>][1,4]diazacyclopentadecine-14 <i>a</i> (5 <i>H</i>)-carboxamide hydrate ritonavir: [5 <i>S</i> -(5 <i>R</i> *,8 <i>R</i> *,10 <i>R</i> *,11 <i>R</i> *)]-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-333: Sodium <i>N</i> -{6-[3- <i>tert</i> -butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2 <i>H</i>)-yl)-2-methoxyphenyl]naphthalen-2-yl}methanesulfonamide hydrate Ribavirin: 1-β- <i>D</i> -ribofuranosyl-1 <i>H</i> -1,2,4-triazole-3-carboxamide	Page:	
Title of Study: An Open-label, Single-Arm, Phase 2 Study to Evaluate the Combination of ABT-450/r/ABT-267 and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Hepatitis C Virus (HCV) Infection taking Methadone or Buprenorphine		
Investigator: Jacob Lalezari, MD		
Study Sites: 8 investigative sites in the United States		

Publications: 1	
Studied Period (Years): First Subject First Visit: 30 April 2013 Last Subject Last Visit: 16 September 2014	Phase of Development: 2
Objective(s): The primary objectives of this study were to assess the safety and efficacy (the percentage of subjects achieving a 12-week sustained virologic response [HCV ribonucleic acid {RNA} < lower limit of quantitation {LLOQ} 12 weeks following therapy] [SVR ₁₂]) of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks in HCV genotype 1-infected adults who were on a stable opioid replacement therapy with methadone or buprenorphine ± naloxone. The secondary objectives of this study were to assess the percentage of subjects with virologic failure during treatment, to assess the percentage of subjects with relapse post-treatment, and to characterize the direct-acting antiviral agent (DAA) pharmacokinetics in HCV-infected subjects on methadone or buprenorphine therapies.	
Methodology: This was a Phase 2, single-arm, open-label, multicenter study evaluating ABT-450/r/ABT-267 and ABT-333 coadministered with RBV in HCV genotype 1-infected adults without cirrhosis who were either pegylated interferon (pegIFN)/RBV treatment-naïve or treatment-experienced, and who were on a stable opioid replacement therapy of methadone or buprenorphine ± naloxone for at least 6 months prior to screening. ABT-450/r/ABT-267 150 mg/100 mg/25 mg was administered orally once daily (QD), and ABT-333 250 mg and RBV were dosed orally twice daily (BID). RBV dosing was weight-based, either 1,000 mg or 1,200 mg daily divided BID per label (e.g., < 75 kg = 1,000 mg daily divided BID or ≥ 75 kg = 1,200 mg daily divided BID). The duration of the study was up to 60 weeks long (not including a screening period of up to 35 days) and consisted of 2 periods: a 12-week Treatment Period and a 48-week Post-Treatment Period (for all subjects who received study drugs). All subjects who received at least 1 dose of study drug were to be followed for 48 weeks post-treatment to monitor for safety, HCV RNA, the emergence and/or persistence of resistant viral variants, and assessment of patient-reported outcome (PRO) instruments. The primary analysis occurred after all subjects had completed through Post-Treatment Week 12 or prematurely discontinued the study. All remaining data through Post-Treatment Week 48 were summarized in the end-of-study analysis.	
Number of Subjects (Planned and Analyzed): Approximately 40 subjects were planned; 38 subjects were enrolled and received at least 1 dose of study drug.	

Diagnosis and Main Criteria for Inclusion:						
Subjects were HCV genotype 1-infected adults (18 to 70 years of age, inclusive) who were either HCV treatment naïve or previous pegIFN/RBV treatment experienced, who were on a stable opioid replacement therapy of methadone or buprenorphine ± naloxone for at least 6 months prior to screening with a body mass index ≥ 18 to < 38 kg/m ² . Females were postmenopausal for at least 2 years, surgically sterile, or of childbearing potential and practicing effective forms of birth control while receiving study drug, practicing total abstinence from sexual intercourse, or sexually active with female partners only. Males must have been surgically sterile, agreed to practice 2 effective methods of birth control throughout the course of the study, or had male partners only. Subjects had chronic HCV infection, a plasma HCV RNA $> 10,000$ IU/mL, a liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis (e.g., a Metavir score of 3 or less or an Ishak score of 4 or less) or FibroTest [®] score ≤ 0.72 and aspartate aminotransferase (AST)-to-platelet ratio index (APRI) ≤ 2 . Subjects with a nonqualifying FibroTest [®] /APRI result would have been allowed to enroll only if they had a qualifying liver biopsy performed within 24 months prior to or during screening.						
Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:						
Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number	
ABT-450/r/ABT-267	AbbVie	Oral	Tablet	75/50/ 12.5 mg	12-008149	
ABT-333	AbbVie	Oral	Tablet	250 mg	12-007842	
Ribavirin	Kadmon Pharmaceuticals, LLC ^a	Oral	Tablet	200 mg	12-007373	
a. DSM Pharmaceuticals Inc. manufactured for Kadmon Pharmaceuticals, LLC.						
Duration of Treatment:						
Subjects received ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks.						
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:						
Not applicable.						
Criteria for Evaluation						
Efficacy:						
HCV RNA in IU/mL was assessed at all Treatment Period visits and at all post-treatment visits.						
Resistance:						
No subject demonstrated virologic failure and no resistance testing was conducted.						
Patient-Reported Outcomes:						
HCV-specific function and wellbeing, and health state utility were assessed using the Short Form 36 Health Survey Version 2 (SF-36v2), the HCV Patient-Reported Outcomes (HCV-PRO) instrument, and the EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L) including the integral visual analogue scale (VAS), respectively.						

Criteria for Evaluation (Continued)

Pharmacokinetic:

Plasma concentrations for ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, and RBV were determined.

Safety:

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

Statistical Methods

Efficacy:

The primary efficacy endpoint was the percentage of subjects with SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drugs). The simple percentage of subjects with SVR₁₂ was calculated, and a 2-sided 95% confidence interval (CI) was calculated using the normal approximation of the binomial.

The secondary efficacy endpoints were: the percentage of subjects with on-treatment virologic failure during the Treatment Period (rebound or failure to suppress during treatment [all on treatment values of HCV RNA ≥ LLOQ] with at least 6 weeks [defined as study drug duration ≥ 36 days] of treatment) and the percentage of subjects with post-treatment relapse (confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of active study drug [up to and including the SVR₁₂ assessment time point] for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment. Completion of treatment was defined as a study drug duration ≥ 77 days).

The simple percentage of subjects with virologic failure and the simple percentage of subjects with post-treatment relapse were calculated, and a corresponding 2-sided 95% CI was calculated using the normal approximation of the binomial.

Patient-Reported Outcomes:

Exploratory analyses of the change in 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 VAS response. Change from baseline in the PRO summary measures was assessed.

The minimally important difference (MID) for the SF-36v2 was a decrease of 5 points from baseline to the Final Treatment Visit for both the Mental Component Summary and Physical Component Summary scores. The percentage of subjects with a change from baseline to the Final Treatment Visit in the Mental Component Summary and Physical Component Summary scores greater (i.e., worse) than the appropriate MID was calculated.

Pharmacokinetic:

Individual plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, and RBV were tabulated and summarized.

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.

Statistical Methods (Continued)

Safety (Continued):

Change from baseline in laboratory tests and vital sign measurements to each time point of collection were 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:

Subjects were administered the 3-DAA regimen of ABT-450/r/ABT-267 + ABT-333 with RBV for 12 weeks. HCV RNA levels were monitored for 48 weeks after the last dose of study drug. SVR₁₂ was achieved by 37/38 (97.4%) subjects, with a 95% CI of 92.3% to 100.0%. The one subject who did not achieve SVR₁₂ and SVR₂₄ prematurely discontinued study drug after 25 days of treatment due to treatment-emergent serious adverse events. Thus, no subject in this study experienced virologic failure. These results suggest that use of chronic methadone or buprenorphine did not adversely affect treatment response.

Resistance Results:

No subject demonstrated virologic failure, and resistance testing was therefore not conducted.

Patient-Reported Outcomes Results:

At least half of subjects experienced decreases (that did not meet criteria to be considered even of minimal importance) or increases from the baseline in their health-related quality of life, function, and wellbeing at the end of treatment.

Pharmacokinetic Results:

The steady-state exposures of ABT-450 were approximately 1.6- to 1.9-fold higher in subjects on methadone compared with subjects on buprenorphine ± naloxone. The observed difference in this small group of subjects could be due to the expected high intersubject variability (> 100% CV) in ABT-450 exposures. Steady-state exposures (area under the plasma concentration-time curve and maximum plasma concentration) of ritonavir, ABT-267, ABT-333, ABT-333 M1, and RBV were comparable or showed modest differences (up to 32%) between subjects on methadone and subjects on buprenorphine ± naloxone. The exposures achieved for ABT-450, ABT-267, ritonavir, ABT-333, ABT-333 M1, and RBV in HCV genotype 1-infected subjects on methadone or buprenorphine ± naloxone in the present study were comparable to or slightly lower than exposures in the Phase 1 studies with the same formulations. Given the efficacy results observed in this study, these small differences in exposures do not appear to be clinically relevant.

Safety Results:

The regimen of ABT-450/r/ABT-267, ABT-333, and RBV was well tolerated in this cohort of subjects on chronic opioid replacement therapy, with only 1 (2.6%) subject prematurely discontinuing DAAs because of treatment-emergent adverse events and no subject experiencing a study drug-related serious adverse event. While the majority of subjects (92.1%) experienced 1 or more treatment-emergent adverse events during the Treatment Period, only 4 (10.5%) subjects experienced severe adverse events. The most common treatment-emergent adverse events were nausea, fatigue, headache, insomnia, rash, anxiety, arthralgia, anemia, irritability, and vomiting.

Summary/Conclusions (Continued)

Safety Results (Continued):

One (2.6%) subject died due to a serious adverse event of acute myeloid leukemia approximately 8 months after taking the last doses of study drug. The investigator considered the event to have no reasonable possibility of relationship to either DAAs or RBV. Two (5.3%) subjects experienced treatment-emergent serious adverse events, which resulted in study drug discontinuation for 1 subject. None of the serious adverse events were considered to be related to DAAs or RBV. No other subject experienced an adverse event leading to premature discontinuation of study drug.

The rate of adverse events of anemia and grade 2 and 3 hemoglobin decreases were numerically greater than those seen in subjects in Study M11-652. This difference appears to be explained by a lower mean hemoglobin level at baseline in the current study, as the mean decrease in hemoglobin seen at the end of study drug treatment in this study (20.9 g/L) was not greater than that seen among treatment-naïve subjects in Study M11-652 receiving a similar regimen (22 g/L).

The bilirubin-related, rash-related, and anemia-related events observed during this study were consistent with other clinical trials of AbbVie DAAs with RBV. No subject had laboratory values that met Hy's law criteria or a grade 2 or greater alanine aminotransferase value.

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

One subject (Subject █████) experienced an event of drug abuse relapse on Day 107 (Post-treatment Day 22) which the investigator considered as having no reasonable possibility of being related to DAAs or RBV.

Conclusions:

A 12-week regimen of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV was generally well tolerated in HCV genotype 1-infected, treatment-naïve or treatment-experienced, noncirrhotic subjects who were on a stable opioid replacement therapy of buprenorphine ± naloxone or methadone, with only a single subject prematurely discontinuing study drug due to adverse events. Antiviral activity was comparable to that seen in subjects not receiving opioid replacement, with 97.4% of subjects achieving SVR₁₂. Adverse events reported in this study were generally consistent with the established safety profile for RBV and those demonstrated for the combination of 3 DAAs with RBV in previous studies.

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