2.0 Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="2">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="2">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
ABT-450, ritonavir, ABT-267, ABT-333, ribavirin</td></tr>
<tr><td>Name of Active Ingredient:
ABT-450 (paritaprevir): (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 (ombitasvir): Dimethyl ([(2S,5S)-1-(4-tert-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate
ABT-333 (dasabuvir): Sodium 3-(3-tert-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1)
Ribavirin: 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide</td><td colspan="2"></td></tr>
<tr><td colspan="3">Title of Study: An Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (Turquoise-IV)</td></tr>
</table>

Coordinating Investigator: Vasily A. Isakov, MD, PhD	
Study Sites: 7 investigative sites in Russia and Belarus	
Publications: None	
Studied Period (Years): First Subject First Visit: 22 September 2014 Last Subject Last Visit: 28 December 2015	**Phase of Development:** 3b

Objectives:

The primary objective of this study was to assess the safety and efficacy (the percentage of subjects achieving a 12-week sustained virologic response, SVR_{12} [HCV ribonucleic acid {RNA} < lower limit of quantification {LLOQ} 12 weeks following treatment]) of coformulated ombitasvir, paritaprevir, and ritonavir (ombitasvir/paritaprevir/r) and dasabuvir coadministered with RBV for 12 weeks in HCV genotype 1b-infected adult subjects with compensated cirrhosis.

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

Methodology:

This was a Phase 3b, open-label, single-arm, multicenter study evaluating the efficacy and safety of ombitasvir/paritaprevir/r and dasabuvir coadministered with RBV for 12 weeks in treatment naïve and pegylated-interferon alfa-2a or alfa-2b (pegIFN)/RBV treatment-experienced, cirrhotic HCV genotype 1b-infected adults.

The duration of the study was up to 36 weeks (not including a screening period of up to 35 days) and consisted of a 12-week Treatment Period and a 24-week Post-Treatment Period for all subjects who received study drugs.

Subjects received ombitasvir/paritaprevir/r 25/150/100 mg once daily (QD) and dasabuvir 250 mg twice daily (BID) with RBV (RBV was administered weight-based 1,000 or 1,200 mg divided BID or 200 mg alternating with 400 mg QD for subjects with creatinine clearance [CrCl] < 50 mL/min) for 12 weeks.

All subjects who received at least 1 dose of study drug were followed for 24 weeks post-treatment to monitor for safety, HCV RNA, and the emergence and persistence of resistant viral variants.

The efficacy analysis occurred after all enrolled subjects completed Post-Treatment Week 24 or prematurely discontinued from the study.

Number of Subjects (Planned and Analyzed): A total of 36 subjects were planned to be enrolled; 36 subjects were enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV GT1b-infected, treatment-naïve or previous pegIFN/RBV treatment-experienced adults (at least 18 years of age) with compensated cirrhosis. Females were either practicing total abstinence from sexual intercourse, sexually active with female partners only, postmenopausal for at least 2 years, surgically sterile, or of childbearing potential and practicing 2 effective forms of birth control while receiving study drug. Males must have been surgically sterile, had male partners only, or agreed to practice 2 effective methods of birth control throughout the course of the study. Subjects had a chronic HCV GT1b infection, a plasma HCV RNA > 1,000 IU/mL, and documentation of cirrhosis (e.g., a Metavir score > 3 or an Ishak score > 4) or FibroScan® result ≥ 14.6 kPa.

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

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
ABT-267/ ABT-450/ Ritonavir	AbbVie	Oral	Tablet	12.5 mg/ 75 mg/ 50 mg	13-001960
ABT-333	AbbVie	Oral	Tablet	250 mg	12-007842
Ribavirin	Roche	Oral	Tablet	200 mg	12-007462

ABT-267/ABT-450/ritonavir = ombitasvir/paritaprevir/r; ABT-333 = dasabuvir

Duration of Treatment: Subjects received ombitasvir/paritaprevir/r and dasabuvir 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 in this study experienced virologic failure; therefore, no resistance testing was conducted.

Pharmacokinetic:

Plasma concentrations of paritaprevir, ritonavir, ombitasvir, dasabuvir, dasabuvir M1 metabolite, and RBV were determined.

Safety:

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

Statistical Methods

Efficacy:

The primary endpoint was the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drugs). The number and percentage of subjects achieving SVR_{12} was calculated and a 2-sided 95% Wilson score confidence interval (CI) for a binomial proportion was computed.

The secondary efficacy endpoints were:

- the percentage of subjects with on-treatment virologic failure (defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, or confirmed increase from nadir in HCV RNA [2 consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir] at any time point during treatment, or failure to suppress [all on-treatment values of HCV RNA ≥ LLOQ] during treatment of at least 6 weeks [≥ 36 days]).

Statistical Methods (Continued)

Efficacy (Continued):

- 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 with HCV RNA < LLOQ at the end of treatment).

The numbers and percentages of the subjects with virologic failure during treatment and with post-treatment relapse were calculated. The corresponding 2-sided 95% Wilson score confidence intervals for a binomial proportion were calculated.

Pharmacokinetic:

Individual plasma concentrations for paritaprevir, ritonavir, ombitasvir, dasabuvir, dasabuvir M1 metabolite, and RBV were tabulated and summarized. Summary statistics were computed based on plasma concentrations by binned time interval since last dose.

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 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-direct-acting antiviral agent (DAA) regimen of ombitasvir/paritaprevir/r + dasabuvir with RBV for 12 weeks. HCV RNA levels were monitored for 24 weeks after the last dose of study drug.

Sustained virologic response 12 and 24 weeks postdosing was achieved by all 36 (100%) subjects.

Resistance Results:

No subject in this study experienced virologic failure; therefore, no resistance testing was conducted.

Pharmacokinetic Results:

The observed geometric mean C_{trough} concentrations of ombitasvir, dasabuvir, and dasabuvir M1 metabolite in pegIFN/RBV treatment-naïve or treatment-experienced HCV genotype 1b-infected adults with compensated cirrhosis in the current study were comparable (≤ 24% change) to the exposures observed in HCV genotype 1-infected adults with compensated cirrhosis in previous Phase 3 studies. Similarly, the observed geometric mean C_{trough} concentration of RBV in the current study was comparable (≤ 7% change) to the observed geometric mean C_{trough} concentrations observed in a previous Phase 3 study conducted in HCV genotype 1-infected adults with compensated cirrhosis. The ranges of DAA and ritonavir exposures from the present study were generally within the ranges from previous Phase 3 studies, though values of paritaprevir and ritonavir were close to the lower end of the ranges from previous Phase 3 studies.

Summary/Conclusions (Continued)

Safety Results:

The regimen of ombitasvir/paritaprevir/r, dasabuvir, and RBV for 12 weeks in HCV genotype 1b, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis was generally well tolerated with no subject prematurely discontinuing study drug because of a treatment-emergent adverse event and no subject experiencing a serious adverse event. No deaths were reported during the study.

While the majority of subjects (61.1%) experienced 1 or more treatment-emergent adverse events during the Treatment Period, only 1 (2.8%) subject experienced a severe adverse event, which was anemia.

The most common treatment-emergent adverse events were anemia, asthenia, cough, and headache.

Review of the specific MedDRA search queries for rash revealed that no subject experienced a treatment-emergent adverse event during the study.

Analysis of hematology parameters showed mean decreases from baseline in hemoglobin, hematocrit, and red blood cells (RBCs), and mean increases in reticulocytes throughout the Treatment Period. The mean decrease from baseline in hemoglobin concentration was 22.9 g/L at the Final Treatment Visit. These mean changes are consistent with the known hemolytic effect of RBV. Mean changes in the remaining hematology parameters were relatively small and not clinically significant.
One (2.8%) subject experienced a grade 3 reduction in hemoglobin. No more than 2 (5.6%) subjects experienced a PCS value for any hematology parameter.

Analysis of chemistry parameters showed that mean changes from baseline to the Final Treatment Visit in chemistry parameters other than liver function tests were relatively small and not clinically significant. PCS values for chemistry parameters were infrequent, occurring in no more than 1 subject, with the exception of total bilirubin.

For total bilirubin, mean increases from baseline were observed at all time points during treatment. By the Post-Treatment Week 4 Visit, the increases in total bilirubin had largely resolved, with mean total bilirubin values below the baseline level. Two subjects had at least a grade 3 total bilirubin value while on treatment, without an associated symptomatic treatment-emergent adverse event.

Mean decreases from baseline were observed in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) at the Final Treatment Visit, Post-Treatment Week 4 Visit, and the Final Post-Treatment Visit. No subject experienced a postbaseline grade 2 or greater ALT elevation.

No events of hepatic decompensation or symptomatic hyperbilirubinemia occurred during the study.

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

Conclusions:

Treatment with a 12-week regimen of ombitasvir/paritaprevir/r and dasabuvir coadministered with RBV in HCV genotype 1b, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis resulted in an SVR_{12} rate of 100%. The regimen was generally well tolerated, with no subject prematurely discontinuing because of a treatment-emergent adverse event and no subject experiencing a serious adverse event. Based on a cross-study comparison in a similar subject population and treatment regimen from a previous Phase 3 study, rates of common adverse events and laboratory abnormalities reported in this study were generally consistent with those observed in the previous Phase 3 study.