2.0 Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir</td></tr>
<tr><td>Name of Active Ingredient:
Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir</td></tr>
<tr><td colspan="3">Title of Study:
An Open-Label Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with Ribavirin in Adults with Genotype 1 and Ombitasvir/Paritaprevir/Ritonavir with Ribavirin in Adults with Genotype 4 Chronic Hepatitis C Virus Infection and Decompensated Cirrhosis (TURQUOISE-CPB)</td></tr>
<tr><td colspan="3">Coordinating Investigator:
[redacted]</td></tr>
<tr><td colspan="3">Study Sites:
13 sites in Canada, the United States of America, and Germany.</td></tr>
<tr><td colspan="3">Publications:
none</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 17 November 2014
Last Subject Last Visit: 03 March 2017</td><td>Phase of Development: 3b</td></tr>
<tr><td colspan="3">Objectives:
The primary objectives of this study were to assess the safety and the SVR_{12} rate of ombitasvir/paritaprevir/ritonavir and dasabuvir with RBV in GT1-infected subjects with decompensated cirrhosis.
The secondary objectives of this study were to assess the safety and the SVR_{12} rate of ombitasvir/paritaprevir/ritonavir with RBV among GT4-infected subjects with decompensated cirrhosis, and to assess separately for each HCV group (Group 1, 2, and 3), the percentage of subjects with virologic failure during treatment, the percentage of subjects with virologic relapse post-treatment, and the percentage of subjects with improvement in laboratory parameters associated with hepatic function including albumin, bilirubin, alpha-fetoprotein, platelet count and international normalized ratio (INR) as well as FibroTest, Child-Pugh, and Model for End-Stage Liver Disease (MELD) scores.</td></tr>
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Methodology:

This was a Phase 3b, open-label, multicenter, multi-country study designed to evaluate the safety and efficacy of ombitasvir/paritaprevir/ritonavir and dasabuvir with RBV in HCV GT1, treatment-naïve and treatment-experienced (previous pegIFN/RBV alone) adults with decompensated cirrhosis. The study also evaluated the safety and efficacy of ombitasvir/paritaprevir/ritonavir with RBV in HCV GT4, treatment-naïve and treatment-experienced (previous peg IFN/RBV alone) adults with decompensated cirrhosis.

The duration of the study was up to 72 weeks (not including the screening period), consisting of a 12-week treatment period for GT1b-infected subjects (Group 1) and a 24-week treatment period for GT1 non-b- and GT4-infected subjects (Groups 2 and 3). Subjects in all treatment groups who received study drug were followed for a 48-week post-treatment (PT) period.

A sentinel cohort of a minimum of 10 GT1 subjects was to be enrolled for an early assessment of safety, viral load, and available pharmacokinetic data which was to occur after all subject in the sentinel cohort reached Treatment Week 12 or prematurely discontinued study treatment. Study enrollment was paused until completion of the sentinel cohort data review.

All subjects who received at least 1 dose of DAA in the treatment period and either completed treatment or prematurely discontinued study drug were to be monitored in the PT period for safety, clinical outcomes, HCV RNA, the emergence and persistence of resistant viral variants and assessment of PROs for an additional 48 weeks following the last does of study drugs.

The primary analysis occurred after all enrolled subjects had completed the Treatment Period through PT Week 12 or had prematurely discontinued from the study. The final analysis occurred after all enrolled subjects completed the study or prematurely discontinued from the study.

Number of Subjects (Planned and Analyzed):

Approximately 60 subjects were planned including approximately 50-GT1 and no more than 10 GT4 subjects with a minimum of 20 subjects in each of Group 1 (GT1b) and Group 2 (GT1 non-b);
36 subjects were enrolled and received at least 1 dose of study drug. There were 9, 24, and 3 subjects in Groups 1, 2, and 3, respectively. Based on postmarketing reports of hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, FDA requested a partial clinical hold for Study M14-227 (03 November 2015). Under the clinical hold, no new subjects were to be enrolled, but already enrolled subjects were permitted to complete treatment.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV GT1 or GT4-infected, treatment-naïve adults (at least 18 years of age). 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, or agreed to practice at least 1 effective method of birth control throughout the course of the study.
Subjects had a HCV GT1- or GT4-infection: positive for anti HCV antibody, a plasma HCV RNA > 1,000 IU/mL at screening, and a laboratory result indicating HCV GT1 or GT4 infection at Screening; documentation of evidence of cirrhosis (e.g., prior liver biopsy, Fibroscan, or radiograph), Child-Pugh score of 7 – 9 (inclusive) at Screening.

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

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
Ombitasvir/ Paritaprevir/ Ritonavir	AbbVie	Oral	Tablet	12.5 mg/ 75 mg/ 50 mg	13-001960, 15-000397
Dasabuvir	AbbVie	Oral	Tablet	250 mg	12-007842, 14-005917
Ribavirin	Roche or Generic Manufacturer	Oral	Tablet	200 mg	14-001215, 12-007699, 12-008082

Duration of Treatment:

Group 1 (GT1b): ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily + dasabuvir 250 mg twice daily + RBV for 12 weeks.

Group 2 (GT1 non-b): ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily + dasabuvir 250 mg + RBV for 24 weeks.

Group 3 (GT4): ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily + RBV for 24 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 all PT visits.

Resistance

The following resistance information was to be provided for the SVR_{12}-achieving subjects who had sequencing performed on baseline samples: the variants at signature resistance-associated amino acid positions at baseline identified by population nucleotide sequencing and comparison to the appropriate prototypic reference sequence.

The following resistance information was to be analyzed for subjects receiving study drugs who did not achieve SVR_{12} and who had HCV RNA $\geq$ 1000 IU/mL: 1) the variants at signature resistance-associated amino acid positions at baseline identified by population nucleotide sequencing and comparison to the appropriate prototypic reference sequence, 2) the amino acid variants in available post-baseline samples identified by population and/or clonal nucleotide sequencing and comparison to baseline sequences, and 3) the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by population nucleotide sequencing and comparison to the appropriate prototypic reference sequence.

Criteria for Evaluation (Continued)

Pharmacokinetic:

Plasma concentrations of paritaprevir, ombitasvir, ritonavir, dasabuvir, dasabuvir M1 metabolite and RBV, as applicable based on DAA regimen, were tabulated.

For the intensive pharmacokinetic data from Week 2, values for the pharmacokinetic parameters of paritaprevir, ombitasvir, ritonavir, dasabuvir, and dasabuvir M1 metabolite, and RBV, as applicable, based on DAA regimen, including the C_{max}, T_{max}, C_{trough}, and AUC were determined by noncompartmental methods.

Patient Reported Outcomes:

The change in general and disease-specific function and wellbeing were assessed using the Short form 36 – Version 2 (SF-36v2) and HCV Patient Report Outcomes (HCV-PRO) instruments, respectively. Health State Utility was measured using the EuroQol-5 Dimensions 5 Level (EQ-5D-5L) instrument. Subjects also rated their perception of their overall health on a separate visual analogue scale (VAS).

Safety:

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

Statistical Methods

Efficacy:

All enrolled subjects who received at least 1 dose of study drug were included in the ITT population (N = 36). All efficacy, patient-reported outcomes, and resistance analyses were performed on the ITT population. In addition, sensitivity analyses of SVR_{12} were performed on the mITT-GT and mITT-GT-VF populations.

The primary endpoint was the percentage of subjects achieving SVR_{12} (HCV < lower limit of quantification (LLOQ) 12 weeks after the last actual dose of study drug) for each GT1 subtype group (Group 1 and Group 2).

The secondary endpoints were: 1) The percentage of GT4 subjects (Group 3) achieving SVR_{12} (HCV < LLOQ 12 weeks after the last actual dose of study drug); 2) The percentage of subjects with virologic failure during treatment for each treatment group; 3) The percentage of subjects with virologic relapse post-treatment for each treatment group; and 4) The percentage of subjects with improvement in laboratory parameters associated with hepatic function including albumin, bilirubin, alpha-fetoprotein, platelet count and INR, as well as FibroTest, Child-Pugh, and MELD scores for each treatment group. The numbers and percentages (with 2-sided 95% confidence intervals using the Wilson score method for the GT1 subtype groups) of subjects with on-treatment virologic failure and post-treatment relapse were calculated for each treatment group. The number and percentage of subjects with improvement in laboratory parameters at PT Week 12 were calculated for each treatment group. The numbers and percentages of subjects who did not achieve SVR_{12} by reason for non-response were calculated for each treatment group.

Statistical Methods (Continued)

Resistance:

The following resistance information was analyzed for all baseline samples from subjects: 1) the prevalence of baseline polymorphisms at signature amino acid positions identified by population sequencing were compared to the appropriate subtype specific prototypic reference sequence; and, 2) a comparison of SVR_{12} rates in subjects with or without baseline polymorphisms was conducted. For subjects not achieving SVR_{12} or SVR_{24}, treatment-emergent substitutions at available postbaseline time points were identified by population nucleotide sequencing or next generation sequencing relative to the respective baseline sequence and to a subtype-specific reference sequence.

Patient-Reported Outcomes:

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 was analyzed by physical and mental component scores. EQ-5D-5L was analyzed by utility score and by visual analogue scale (VAS) response. Mean changes from baseline in PRO scores to each applicable post-baseline time point were summarized for each treatment group. The number and percentage of subjects with a decrease that was less than the minimally important difference (MID) from baseline to the Final Treatment Visit for the SF-36v2 component summary scores were calculated for each treatment group.

Pharmacokinetic:

Plasma concentrations of paritaprevir, ombitasvir, dasabuvir, dasabuvir M1 metabolite, ritonavir and RBV, as applicable based on DAA regimen, were tabulated for each subject. Summary statistics were computed for each time point (for intensive pharmacokinetic data) or binned time interval (for sparse pharmacokinetic data).

For the intensive pharmacokinetic data, values for the pharmacokinetic parameters of paritaprevir, ombitasvir, ritonavir, dasabuvir, and dasabuvir M1 metabolite, and RBV, as applicable based on DAA regimen, including the C_{max}, T_{max}, C_{trough}, and AUC were calculated and tabulated for each analyte.

Safety:

The number and percentage of subjects reporting treatment-emergent adverse events (TEAEs) were tabulated by Medical Dictionary for Regulatory Activities (MedDRA®) system organ class (SOC) 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.

Changes from baseline in laboratory tests and vital sign measurements to each time point of collection during the Treatment Period were summarized. Laboratory and vital sign values that were potentially clinically significant, according to predefined criteria, were identified, and the percentages of subjects with values meeting these criteria during the Treatment Period were calculated. Hemoglobin and liver function tests were also categorized using Common Terminology Criteria for Adverse Events (CTCAE) grades, and the percentages of subjects with values within each CTCAE grade level were calculated.

The number and percentage of subjects experiencing clinical outcome events during treatment and through PT Weeks 12, 24, and 48 were calculated. The following events were considered to be clinical outcome events: death, liver decompensations (ascites, hepatic encephalopathy, or variceal bleeding), hepatocellular carcinoma, and liver transplantation.

Summary/Conclusions

Efficacy Results:

This was an open-label study of 36 HCV GT1 or GT4-infected subjects with decompensated cirrhosis (Child-Pugh B) who were treated with ombitasvir/paritaprevir/ritonavir with or without dasabuvir and with RBV for 12 weeks or 24 weeks (12 weeks only for GT1b-infected subjects with decompensated cirrhosis).

SVR_{12} was achieved in 9 of 9 (100%) GT1b subjects, 23 of 24 (95.8%) GT1 non-B subjects, and 2 of 3 (66.7%) GT4 subjects. While some differences in SVR_{12} rates were observed across subgroups based on demographic and baseline characteristics (e.g., fibrosis status, prior HCV treatment status, IFN eligibility) in various analyses, these were generally small and not considered clinically significant partly due to limited sample sizes. No subject experienced on-treatment virologic failure, 1 subject relapsed during the SVR_{24} assessment window, and no subject relapsed thereafter.

A majority of subjects experienced an improvement in Child Pugh score (19/33; 58%) from baseline to Post-Treatment Week 12, while 22/31 (71%) had an improvement of the MELD score over the same duration.

Resistance Analyses:

Baseline polymorphisms in NS3, including those at position 80 in GT1a, were detected in 58.3% (21/36) of the GT1a-, GT1b-, GT4a- and GT4d-infected subjects. Baseline polymorphisms in NS5A were detected in 25.0% (9/36) of the GT1a-, GT1b-, GT4a- and GT4d-infected subjects. Baseline polymorphisms in NS5B were detected in 6.1% (2/33) of the GT1a- and GT1b-infected subjects. Baseline polymorphisms in NS3, NS5A or NS5B had no impact on treatment outcome as no subject experienced virologic failure in the study.

Pharmacokinetic Results:

In HCV-infected subjects with Child-Pugh B, the exposures of paritaprevir and dasabuvir were higher than in those with compensated cirrhosis or without cirrhosis, while the ombitasvir exposures were lower.

Safety Results:

Most AEs were mild or moderate in severity. Nausea, fatigue, diarrhea, and ascites were the most frequently reported AEs.

There was 1 treatment-emergent death due to decompensated liver disease, 1 death during the PT Period due to cholangiocarcinoma, and 1 subject had a liver transplantation in the PT Period.

A total of 8 subjects had AEs that led to premature discontinuation of study drug. All but 1 of these subjects achieved SVR_{12}.

RBV dose modification was required for 19 subjects due to AEs, mostly as a result of decreases in hemoglobin or anemia.

Hepatic decompensation events occurred in 19 subjects by PT Week 12. Most of these events occurred in subjects with a prior history of the same decompensating events. A total of 4 subjects discontinued treatment due to a decompensation event, and 2 subjects discontinued treatment due to hyperbilirubinemia.

Summary/Conclusions (Continued)

Conclusions:

- HCV GT1 subjects with Child-Pugh B decompensated cirrhosis achieved a high SVR_{12} rate with ombitasvir/paritaprevir/ritonavir with dasabuvir and ribavirin. The number of GT4-infected subjects was small (n = 3), thus no conclusion can be made for this subject population.
- In general, measures of hepatocyte function improved for the majority of patients.
- Most AEs were mild or moderate in severity. Serious adverse events were common in this population; however, most events did not result in discontinuation of therapy.
- Approximately half of the subjects in this trial experienced hepatic decompensation events, most of whom had a history of the same decompensating event.
- These data suggest that the use of ombitasvir/paritaprevir/ritonavir with or without dasabuvir and with ribavirin in patients with Child-Pugh B cirrhosis may be associated with an elevated risk of hepatic decompensation.