Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir		
Name of Active Ingredient: Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir		
Title of Study: An Open Label, Single Arm Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir in Treatment-Naïve Adults With Genotype 1b Hepatitis C Virus (HCV) Without Cirrhosis (GARNET)		
Coordinating Investigator: [redacted]		
Study Sites: 20 sites in Australia, Canada, United Kingdom, Spain, Germany, France, Italy, and Israel.		
Publications: none		
Studied Period (Years): First Subject First Visit: 24 November 2015 Last Subject Last Visit: 01 December 2016	**Phase of Development:** 3b	
Objectives: The primary objective of this study was to assess the efficacy (the percentage of subjects achieving SVR_{12} [HCV ribonucleic acid {RNA} < lower limit of quantification {LLOQ} 12 weeks following treatment]) of coformulated ombitasvir/paritaprevir/ritonavir and dasabuvir (3-DAA) for 8 weeks in treatment-naïve adults with HCV GT1b infection without cirrhosis. The secondary objectives of this study were to assess the percentage of subjects with virologic failure during treatment, the percentage of subjects with virologic relapse post-treatment, the percentage of female subjects with SVR_{12}, and the percentage of subjects with low baseline viral load (HCV RNA < 6,000,000 IU/mL) with SVR_{12} in previously untreated adults with HCV GT1b infection.		

Methodology:

This was a Phase 3b, open-label, single-arm, multicenter study evaluating the safety and efficacy of the 3-DAA regimen administered for 8 weeks in HCV GT1b-infected, treatment-naïve adults without cirrhosis.

The duration of the study was up to 32 weeks (not including the screening period), consisting of an 8-week Treatment Period (TP) and a 24-week post treatment (PT) period for all subjects who received study drugs.

All subjects who received at least 1 dose of study drug were to be followed for 24 weeks PT to monitor for safety, HCV RNA, and the emergence and persistence of resistant viral variants and assessment of Patient-Reported Outcome (PRO) measurements.

The primary analysis occurred after all subjects had completed through PT Week 12 or prematurely discontinued the study. All remaining data through PT Week 24 were summarized in the end-of-study analysis.

Number of Subjects (Planned and Analyzed):

Approximately 160 subjects were planned, 166 subjects were enrolled and received at least 1 dose of study drug. A minimum of 80 female subjects were planned, 94 female subjects were enrolled and received at least 1 dose of study drug. A minimum of 80 subjects with low baseline viral load (HCV RNA < 6,000,000 IU/mL) were planned, 154 subjects with low baseline viral load were enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV genotype 1b-infected, treatment-naïve adults (at least 18 years of age) without 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, or agreed to practice at least 1 effective method of birth control throughout the course of the study. Subjects had a chronic HCV genotype 1b infection, a plasma HCV RNA > 1,000 IU/mL at screening, and documentation of absence of cirrhosis (e.g., liver biopsy demonstrating absence of cirrhosis, a Metavir score ≤ 3 or an Ishak score ≤ 4, FibroScan® result < 12.5 kPa, or FibroTest score of ≤ 0.72 and aspartate aminotransferase to platelet ratio index [APRI] ≤ 2).

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	14-005707
Dasabuvir	AbbVie	Oral	Tablet	250 mg	14-001469

Duration of Treatment:

Subjects received ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily and dasabuvir 250 mg twice daily for 8 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 TP visits and all PT visits.

Resistance:

The following resistance information was provided for all subjects with an available baseline sample with HCV RNA ≥ 1000 IU/mL: the amino acid variants at baseline at signature resistance-associated positions identified by population nucleotide sequencing and comparison to the reference sequence. The following resistance information was tabulated and summarized for subjects who experienced virologic failure and who had an available post-baseline sample with HCV RNA ≥ 1000 IU/mL: 1) the amino acid variants at each position identified by population sequencing and comparison to the baseline sequence, and 2) the amino acid variants at signature resistance-associated positions identified by population sequencing and comparison to the reference sequence.

Patient-Reported Outcomes:

The change in disease-specific function and wellbeing were assessed using the Patient-Reported Outcome (PRO) instruments. 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). Fatigue was measured using the Fatigue Severity Scale (FSS) instrument.

Safety:

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

Statistical Methods

Efficacy:

All enrolled subjects who received at least 1 dose of study drug were included in the intent-to-treat (ITT) population (N = 166). Efficacy analyses were performed on the ITT population. Sensitivity analyses of the primary and secondary efficacy endpoints were performed on the mITT-GT population (N = 163), which excluded subjects without GT1b according to the central laboratory or phylogenetic analysis.

The primary endpoint was the number and percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). The number and percentage of subjects with SVR_{12} was summarized along with a 2-sided 95% confidence interval (CI) using the normal approximation to the binomial distribution.

Statistical Methods (Continued)

Efficacy (Continued):

The secondary efficacy endpoints were: 1) The percentage of subjects with baseline HCV RNA < 6,000,000 IU/mL with SVR_{12}; 2) The percentage of female subjects with SVR_{12}; 3) The percentage of subjects with on-treatment virologic failure, defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, or confirmed increase of at least 1 $\log_{10}$ IU/ml from nadir during treatment, failure to suppress during treatment (all on-treatment values of HCV RNA ≥ LLOQ) among subjects with at least 6 weeks (active study drug duration ≥ 36 days) of treatment; and 4) The percentage of subjects with PT relapse, defined as confirmed HCV RNA ≥ LLOQ between end of treatment (EOT) and 12 weeks after last dose of study drug (up to and including the SVR_{12} assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment. Completion of treatment is defined as a study drug duration ≥ 51 days. For all secondary endpoints, the corresponding 2-sided 95% confidence intervals were also provided using the normal approximation to the binomial distribution. For both the primary and secondary endpoints, if the rate was 0% or 100%, the Wilson's score method for a single binomial proportion was used to create the 95% confidence interval.

The number and percentage of subjects with SVR_{12} were presented for additional subgroups (age, race, sex, ethnicity, BMI, baseline HCV RNA levels, fibrosis stage, geographic region, country, former injection drug use, IL28B genotype, history of bleeding disorders, history of depression or bipolar disorder, history of hypertension, and subject compliance with 3-DAA treatment). Each subgroup analysis was performed if there were an adequate number of subjects within the subgroup. The 2-sided 95% confidence interval using normal approximation to the binomial was produced if there were at least 10 subjects in the subgroup.

Resistance:

The following resistance information was analyzed: the polymorphisms at signature amino acid positions at baseline identified by population nucleotide sequencing were compared to the appropriate prototypic reference sequence; a comparison of SVR rates for subjects with and without baseline polymorphisms at signature amino acid positions in NS3, NS5A, and NS5B was provided; the amino acid substitutions at available post-baseline time points identified by population and/or next generation sequencing were compared to baselin or the appropriate prototypic reference sequences; and persistence analysis of treatment-emergent substitutions was provided.

Patient-Reported Outcomes

Summary statistics (N, mean, standard deviation, median, minimum and maximum) of values at each visit and change from baseline to each visit were provided for the EQ-5D-5L health index, VAS scores, and the FSS total score.

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.

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:

Sustained virologic response 12 weeks post dosing (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) was achieved by 162/166 (97.6%; 95% CI 95.3% to 99.9%) subjects in the ITT population and 160/163 (98.2%; 95% CI 96.1% to 100.0%) subjects in the mITT-GT population.

The rates of virologic failure during treatment and relapse by PT Week 12 were very low in HCV GT1b-infected subjects (0/163 and 2/161 [1.2%], respectively). The rate of female, HCV GT1b-infected subjects who achieved SVR_{12} was 97.8% (91/93). A total of 98.7% (149/151) of HCV GT1b-infected subjects with low baseline viral load (HCV RNA < 6,000,000 IU/ml) achieved SVR_{12}.

Among GT1b-infected subjects with fibrosis stage F3 who were treated with study drug for 8 weeks, 86.7% (13/15) achieved SVR_{12}. Fibrosis stage was the only baseline factor identified as being associated with SVR_{12}; fibrosis stage F3 was associated with lower odds of achieving SVR_{12} compared to fibrosis stage F0-F2.

Among subjects who received SVR_{12}, no subject subsequently relapsed. One subject failed to achieve SVR_{24} due to reasons other than virologic failure (missing data in the SVR_{24} analysis window).

Patient-Reported Outcomes Results:

In general, subjects treated with ombitasvir/paritaprevir/ritonavir and dasabuvir did not experience worsening of PRO scores from baseline to the Final Treatment Visit or the PT Week 24 Visit.

Resistance Results:

Inhibitor class-specific baseline polymorphisms were rare in NS3 and were observed at a prevalence of 27.1% (42/155) in NS5A, 40% (62/155) in NS5B, of which 11.6% (18/155) had polymorphisms across both NS5A and NS5B. Presence of baseline polymorphisms had no impact on SVR_{12} rates. Among HCV GT1b-infected subjects, 2 subjects demonstrated virologic failure, both were post-treatment relapses. One subject had baseline regimen-specific polymorphisms in NS5A (L31M) and NS5B (C316N and S556G), and had treatment-emergent substitution Y93C in NS5A, but had no treatment-emergent substitutions in NS3 or NS5B. Treatment-emergent substitution Y93C in NS5A persisted through Post Treatment Week 24. The other subject who experienced post-treatment relapse had no regimen-specific polymorphisms at baseline or any treatment-emergent substitutions at the time of virologic failure in any target.

Safety Results:

Ombitasvir/paritaprevir/ritonavir and dasabuvir for 8 weeks in HCV GT1b, treatment-naïve adults without cirrhosis was generally well tolerated, demonstrating a favorable safety profile and no new safety signals. Most subjects had TEAEs that were mild in severity. The most common TEAEs were headache, fatigue, nasopharyngitis, and pruritus. No subject experienced a serious adverse event that was considered possibly related to DAAs. Treatment-emergent adverse events leading to premature discontinuation of study drug were rare, occurring in < 1% of subjects. Laboratory abnormalities were infrequent; only 1 subject (< 1%) discontinued study drug due to hyperbilirubinemia and ALT elevation. No clinically meaningful results of vital signs or ECGs were observed.

Conclusions:

Treatment with an 8-week regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir is an appropriate treatment option for HCV GT1b-infected, treatment-naïve subjects without advanced fibrosis or cirrhosis.

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