2.0 Synopsis

<table>
<tr><td>AbbVie GK</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:
paritaprevir/ritonavir/ombitasvir (ABT-450/r/ABT-267)</td></tr>
<tr><td>Name of Active Ingredient:
<u>Paritaprevir (ABT-450):</u>
(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,14,15,16,16atetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate
<u>Ritonavir:</u>
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-thiazolylmethylester, [5S-(5R*,8R*,10R*,11R*)]
<u>Ombitasvir (ABT-267):</u>
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</td></tr>
<tr><td colspan="3">Title of Study:
An Open-Label Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) Co-administered with Ribavirin (RBV) for 12 or 16 Weeks in Treatment-Naïve and Treatment-Experienced Japanese Adults with Genotype 2 Chronic Hepatitis C Virus (HCV) Infection With and Without Compensated Cirrhosis (GIFT-II)</td></tr>
<tr><td colspan="3">Coordinating Investigator:
Ken Sato, MD, PhD</td></tr>
<tr><td colspan="3">Study Sites:
A total of 53 investigative sites in Japan; 5 study sites did not enroll any subjects.</td></tr>
</table>

Publications: Not applicable	
Studied Period (Years): First Subject First Visit: 14 January 2014 Last Subject Last Visit: 24 September 2015	**Phase of Development:** 3

Objectives:

The primary objectives of this study were to compare the SVR_{12} rates (the percentage of subjects achieving a 12-week sustained virologic response, SVR_{12}, [HCV RNA < lower limit of quantification {LLOQ} 12 weeks following therapy]) of 12 weeks and 16 weeks of treatment with ABT-450/r/ABT-267 coadministered with RBV to a clinically relevant threshold, based on the historical SVR rate of pegylated interferon (pegIFN)/RBV therapy in treatment-naïve, noncirrhotic, HCV GT2-infected Japanese subjects and to assess the safety of the direct-acting antiviral agent (DAA) combination regimen with RBV administered for 12 and 16 weeks in HCV GT2-infected Japanese subjects.

The secondary objectives of this study were to assess, for each treatment duration, the percentage of subjects with on-treatment virologic failure, the percentage of subjects with relapse, and the percentage of subjects with SVR_{12} within different subpopulations.

Methodology:

This was a Phase 3, randomized, open-label, multicenter study evaluating the efficacy and safety of ABT-450/r/ABT-267 co-administered with weight-based RBV for 12 or 16 weeks in adult chronic HCV GT2-infected treatment-naïve and IFN treatment-experienced subjects with and without compensated cirrhosis.

A total of 171 HCV GT2-infected (on the basis of the LiPA 2.0 assay) treatment-naïve and treatment-experienced Japanese subjects in 48 sites were randomized in a 1:1 ratio into 2 arms:

Arm A: ABT-450/r/ABT-267 150/100/25 mg once daily + RBV* for 12 weeks;

Arm B: ABT-450/r/ABT-267 150/100/25 mg once daily + RBV* for 16 weeks.

* RBV = weight-based RBV, 400 mg to 1000 mg daily divided BID, as per local label.

The randomization was stratified by presence of compensated cirrhosis (noncirrhotic, cirrhotic). The randomization for noncirrhotic subjects was also stratified by prior HCV medication history (treatment-naïve, treatment-experienced with an IFN-based therapy) and further stratified by type of response to previous IFN-based treatment (nonresponder, relapser, or intolerant to IFN-based therapy) for treatment-experienced subjects.

Approximately 80 noncirrhotic, treatment-naïve, 60 noncirrhotic treatment-experienced and 10 cirrhotic subjects were planned to be randomized. Among the treatment-experienced subjects, approximately 10 nonresponders, approximately 30 relapsers and approximately 20 subjects intolerant to IFN-based therapy were planned to be randomized.

The duration of the study was up to 64 weeks, depending on treatment assignment, (not including a screening period of up to 35 days) consisting of 2 periods: the Treatment Period and the Post-Treatment Period. In the Treatment Period, subjects received either 12 or 16 weeks of therapy. In the Post-Treatment Period, all subjects who received at least 1 dose of study drugs were to be followed for 48 weeks to monitor for safety, HCV RNA, the emergence and/or persistence of resistant viral variants, and assessment of patient-reported outcomes (PROs).

Number of Subjects (Planned and Analyzed):

Approximately 150 subjects were planned to be randomized in the study. A total of 171 subjects were randomized and received at least 1 dose of study drugs.

Diagnosis and Main Criteria for Inclusion:

All subjects were included as follows:

Subjects were Japanese males or females between the ages of 18 and 75 years.

All subjects had chronic HCV GT2 infection prior to study enrollment (determined by the LiPA 2.0 assay), with plasma HCV RNA > 10,000 IU/mL at screening.

Females were postmenopausal for at least 2 years, surgically sterile, or of childbearing potential, had negative urine pregnancy test results at screening and baseline, were using at least 1 effective method of birth control at the time of informed consent form (ICF) sign-off, and agreed to use 2 effective forms of birth control from the time of ICF sign-off, during study drug administration, and for 6 months after stopping study drug. Males were surgically sterile or practicing 2 effective methods of birth control throughout the course of the study, starting with Study Day 1 through 6 months after stopping study drug.

Noncirrhotic subjects were included as follows:

Absence of cirrhosis was demonstrated by the results of liver biopsy within 24 months prior to or during screening (e.g., METAVIR or New Inuyama fibrosis score ≤ 3 or an Ishak fibrosis score ≤ 4), or if no liver biopsy was available, a FibroTest® score ≤ 0.72 and aspartate aminotransferase to platelet ratio index (APRI) ≤ 2; a screening transient elastography (e.g., FibroScan®) result < 12.5 kPa; or a Discriminant Score less than zero.

Noncirrhotic, treatment-naïve subjects were defined as noncirrhotic subjects who had never received any HCV treatment and met 1 of the following categories:

- Naïve IFN-eligible subject was defined as naïve subject who was considered by the investigator to be a good candidate to receive an IFN-based therapy (IFN [alpha, beta or pegIFN] with or without RBV); or
- Naïve IFN-ineligible subject was defined as naïve subject who was considered by the investigator to be a poor candidate to receive an IFN-based therapy (IFN [alpha, beta or pegIFN] with or without RBV), due to medical reasons, such as, but not limited to, advanced age, depression, myelosuppression, diabetes, autoimmune disease, retinopathy, or cardiovascular or renal dysfunction.

Noncirrhotic, treatment-experienced subjects were defined as subjects who had documentation of prior IFN-based therapy (IFN [alpha, beta or pegIFN] with or without RBV) and met 1 of the following categories:

- Nonresponder: received at least 12 weeks of IFN-based therapy for the treatment of HCV and failed to achieve undetectable HCV RNA (HCV RNA < lower limit of detection [LLOD]) at the end of treatment; or
- Relapser: received IFN-based therapy for the treatment of HCV and was undetectable at or after the end of treatment, but subsequently had detectable HCV RNA within 52 weeks of treatment follow-up; or
- IFN-intolerant: treatment of HCV was discontinued during the treatment period due to intolerance to any of the components of the IFN-based therapy.

Diagnosis and Main Criteria for Inclusion (Continued):

Subjects with compensated cirrhosis were included as follows:

Presence of cirrhosis was demonstrated by the results of liver biopsy within the 24 months prior to or during the screening (e.g., METAVIR or New Inuyama fibrosis score > 3 [including 3 – 4 or 3/4] or an Ishak fibrosis score > 4) or if no liver biopsy was available, a FibroTest score ≥ 0.73 and APRI > 2; a screening transient elastography (e.g., FibroScan) result ≥ 14.6 kPa; or a Discriminant Score greater than zero. Subjects had compensated cirrhosis, as defined by a Child-Pugh score of ≤ 6 at screening.

Cirrhotic treatment-naïve subjects were as defined as cirrhotic subjects who had never received any HCV treatment.

Cirrhotic, treatment-experienced subjects were defined as subjects who had documentation of prior IFN based therapy (IFN [alpha, beta or pegIFN] with or without RBV) and completed no less than 2 months prior to the Screening Visit. Cirrhotic subjects were required to have absence of hepatocellular carcinoma based on ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI) within 3 months prior to screening.

Subjects with a FibroScan result ≥ 12.5 kPa and < 14.6 KPa, a FibroTest ≤ 0.72 with an APRI > 2, a FibroTest result ≥ 0.73 with an APRI ≤ 2, or a Discriminant Score = 0 were classified as cirrhotic or noncirrhotic based the result of a liver biopsy performed within 24 months prior to screening or during screening.

All subjects were excluded as follows:

- Females who were pregnant or planned to become pregnant, or breastfeeding.
- Co-infected with hepatitis B virus (HBV) or human immunodeficiency virus (HIV).
- Use of contraindicated medication(s) within 2 weeks prior to study drug administration or 10 half-lives (if known), whichever was longer.
- Use of known strong inducers (e.g., phenobarbital, rifampin, carbamazepine, St. John's Wort) of cytochrome P450 3A (CYP3A) within 2 weeks prior to initial study drug administration.
- Any cause of liver disease other than chronic HCV infection, including but not limited to: hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease, autoimmune hepatitis, alcoholic liver disease or drug-related liver disease.
- An estimated glomerular filtration rate (eGFRj) < 60 mL/min/1.73 m^2, as estimated by the modification of diet in renal disease (MDRD) method, modified for the Japanese population.

Noncirrhotic subjects were excluded as follows:

- Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis.
- Platelets < 100,000 cells/mm^3.

Subjects with compensated cirrhosis were excluded as follows:

- Any current or past clinical evidence of a Child-Pugh B or C Classification or any clinical history of liver decompensation, such as ascites (noted on physical exam), variceal bleeding or hepatic encephalopathy.
- Platelet count < 70,000 cells/mm^3.
- Serum alpha fetoprotein > 100 ng/mL at Screening.
- Confirmed presence of hepatocellular carcinoma on imaging technique.

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/ritonavir/ ABT-267	AbbVie	Oral	Tablet	75/50/12.5 mg	13-004118
Ribavirin	MSD	Oral	Capsule	200 mg	P010M, P012R

Duration of Treatment:

Subjects received 2-DAA + RBV for 12 or 16 weeks.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Not applicable.

Criteria for Evaluation

Efficacy:

The primary endpoints were:

1. SVR_{12}: Among treatment-naïve, noncirrhotic subjects, superiority of Arm B to a clinically relevant threshold; lower bound of 95% confidence interval (LCB) had to exceed 67% to achieve superiority.
2. SVR_{12}: Among treatment-naïve, noncirrhotic subjects, superiority of Arm A to a clinically relevant threshold; lower bound of 95% confidence interval (LCB) had to exceed 67% to achieve superiority.

The primary endpoints were tested at an alpha level of 0.05 using the hierarchical order outlined above to control Type I error.

Secondary endpoints included the following:

- On-treatment virologic failure in each treatment arm: confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point during treatment after HCV RNA < LLOQ, confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment or HCV RNA ≥ LLOQ persistently during treatment with at least 6 weeks (≥ 36 days) of treatment.
- Relapse in each treatment arm: confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) between the Final Treatment Visit and 12 weeks after the last dose of study drug among subjects completing treatment with HCV RNA < LLOQ at the Final Treatment Visit and at least one post-treatment HCV RNA value.
- SVR_{12} in each treatment arm within the following subpopulations:
  - Noncirrhotic treatment-experienced subjects who relapsed after prior IFN-based therapy
  - Noncirrhotic treatment-experienced subjects who were non-responders to prior IFN-based therapy
  - Noncirrhotic treatment-experienced subjects who were intolerant to IFN-based therapy
  - Subjects with compensated cirrhosis

Criteria for Evaluation (Continued)

Resistance:

For all subjects who received study drugs, the variants at signature resistance-associated amino acid position by population nucleotide sequencing at baseline compared to the appropriate prototypic reference sequence were tabulated and summarized. For subjects not achieving SVR, the variants at each amino acid position by population and/or clonal nucleotide sequencing at available post-baseline time points compared to baseline and the appropriate prototypic reference sequences were tabulated and summarized.

Pharmacogenetic:

IL28B status (CC, CT, or TT) was determined for each subject and analyzed as a factor contributing to the subject's response to study treatment.

Patient-Reported Outcomes:

Exploratory analyses included mean change from baseline in HCV-PRO total score to each applicable post-baseline time point and mean change from baseline in EQ-5D-5L health index score and VAS score to each applicable post-baseline time point.

Pharmacokinetic:

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

Safety:

Safety and tolerability were assessed throughout the study on the basis of adverse event monitoring and vital signs, physical examination, ECG, and laboratory tests assessments.

Statistical Methods

Efficacy, safety and demographic analyses were performed on all subjects who received at least 1 dose of study drug.

The Post-Treatment Week 24 analysis occurred after subjects had completed the Post-Treatment Week 24 Visit or prematurely discontinued from the study and was presented in an interim study report. This final study report presents the end of study analysis and includes all final data through the end of the study (through Post-Treatment Week 48).

No data were imputed for any efficacy or safety analysis, except for PRO, rapid virologic response (RVR), end of treatment response (EOTR), and SVR endpoints.

Efficacy:

Plasma HCV RNA levels were determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT PCR) assay v2.0. For this assay, the lower limit of detection (LLOD) was 15 IU/mL and LLOQ was 25 IU/mL. HCV RNA results that were detectable but not quantifiable were reported as "< 25 IU/ML HCV RNA DETECTED" and those that are undetectable were reported as "HCV RNA NOT DETECTED" in the database.

Statistical Methods (Continued)

Efficacy (Continued):

Primary Endpoint

The following hypothesis was tested on the subset of subjects in the primary efficacy population. To test the hypothesis that the percentage of noncirrhotic, treatment-naïve HCV GT2-infected subjects treated with ABT-450/r/ABT-267 + RBV for 12 or 16 weeks who achieve SVR_{12} is superior to a clinically acceptable threshold (based on historical SVR rates for the corresponding population treated with pegIFN/RBV therapy), the percentage of subjects with SVR_{12} was calculated for each treatment arm with a 2-sided 95% confidence interval (CI). The CI was calculated using the normal approximation to the binomial distribution. The lower bound of the 2-sided 95% confidence interval must be greater than 67% in order for the regimen to be considered superior to the clinically acceptable threshold in the population of noncirrhotic, treatment-naïve, HCV GT2-infected subjects (by LiPA assay). Additionally, a 2-sided 95% CI for the SVR_{12} rate was calculated using the Wilson score method for a single proportion. In the case of 100% SVR_{12} rate, the lower bound of the confidence interval based on the Wilson score method was used to compare to the threshold of 67%.

Secondary Endpoints

The number and percentage of subjects with on-treatment virologic failure, the number and percentage of subjects with relapse and the number and percentage of subjects achieving SVR_{12} within each specified subgroup were summarized for each treatment arm, along with 95% CIs using the Wilson score method. On-treatment virologic failure and relapse were summarized separately for the primary efficacy population, and for each subpopulation specified for the third secondary endpoint.

Resistance:

The following resistance information was analyzed for subjects receiving active drugs who did not achieve SVR:

1. The variants at signature resistance-associated amino acid position at baseline identified by population nucleotide sequencing were compared to the appropriate prototypic reference sequence,
2. The variants at available post-baseline time points identified by population and/or clonal nucleotide sequencing were compared to baseline and the appropriate prototypic reference sequences,
3. The most prevalent amino acid variants found by population sequencing and amino acid variants that emerged or became enriched in isolates from at least 2 subjects of the same subgenotype were summarized, and
4. A comparison of SVR rates for subjects with and without baseline variants at the positions of interest in NS3 and NS5A was provided, and
5. Persistence analysis of resistance-associated variants was provided.

Pharmacokinetic:

Plasma concentrations of ABT-450, ritonavir, ABT-267, and RBV were tabulated for each subject and group.

Statistical Methods (Continued):

Safety:

The number and percentage of subjects having treatment-emergent adverse events (TEAE, defined as any event that began or worsened in severity after initiation of study drug through 30 days post-study drug dosing) were tabulated by primary MedDRA System Organ Class and preferred term for each treatment arm. Pairwise comparisons of the percentages of subjects with TEAEs were made between treatment arms using Fisher's exact tests. The tabulation of the number of subjects with TEAEs also was provided with further breakdown by severity rating and relationship to study drug.

Subjects reporting more than 1 adverse event for a given MedDRA preferred term were counted only once for that term using the most severe incident for the severity rating table. Subjects reporting more than 1 type of event within a System Organ Class were counted only once for that System Organ Class.

Laboratory and vital sign values that were potentially clinically significant (PCS), according to predefined criteria, were identified and the percentages of subjects with PCS values during the Treatment Period were compared between arms using Fisher's exact tests.

Summary/Conclusions

Efficacy Results:

SVR_{12} rates were 91.5% (43/47) in Arm B (95% CI: 83.5% to 99.5%) and 75% (36/48) in Arm A (95% CI: 62.8% to 87.2%) in the primary efficacy population. The LCB was above 67% (superiority threshold) for Arm B but not for Arm A. Therefore, 16-week treatment with 2-DAA + RBV demonstrated superiority to the clinically relevant threshold (based on historical SVR rates for pegIFN/RBV therapy in treatment-naïve, noncirrhotic subjects). Sensitivity analyses to evaluate alternative methods to impute missing post-treatment virologic results in the primary efficacy population yielded results consistent with those of the primary efficacy analysis.

Secondary efficacy endpoint results were as follows:

- Similar to the pattern observed in the primary efficacy population, similar proportions of subjects of both study Arms experienced on-treatment virologic failure while post-treatment relapse was observed in Arm A only.
  - On-treatment virologic failure occurred in 15.3% (13/85) of subjects in Arm A and in 16.3% (14/86) of subjects in Arm B.
  - Relapse by Post-Treatment Week 12 occurred in 10.1% (7/69) of subjects in Arm A and no subject in Arm B.
- Among treatment-experienced subjects, SVR_{12} rates were highest among subjects who relapsed after previous IFN-based therapy and were generally higher in Arm B than Arm A within the different subpopulations.
  - Among treatment-experienced, noncirrhotic subjects who relapsed after prior IFN-based therapy, SVR_{12} rates were 80.0% (12/15) in Arm A and 93.8% (15/16) in Arm B.
  - In treatment-experienced, noncirrhotic subjects who were nonresponders to prior IFN-based therapy, SVR_{12} rates were 40.0% (2/5) in Arm A and 50.0% (3/6) in Arm B.
  - In treatment-experienced, noncirrhotic subjects who were intolerant to IFN-based therapy; SVR_{12} rates were 66.7% (8/12) in Arm A and 63.6% (7/11) in Arm B.
- In subjects with compensated cirrhosis, SVR_{12} rates were 80.0% (4/5) in Arm A and by 33.3% (2/6) in Arm B.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Stepwise logistic regression models were fitted to subjects in the ITT population to assess the associations between subgroup variables and SVR_{12} or virologic failure. The following subgroup variables were identified as having a statistically significant ($P < 0.10$) association with SVR_{12}: HCV GT2 subtype (subjects with HCV GT2a infection had higher odds of SVR_{12} than those with HCV GT2b infection), prior HCV treatment experience (treatment-naïve subjects had higher odds of SVR_{12} than treatment-experienced subjects), and RBV dose reduction modification (subjects with RBV dose modification had higher odds of SVR_{12} than those without RBV dose modification).

SVR_{12} rates in noncirrhotic subjects were consistently higher in subjects with HCV GT2a infection than in those with HCV GT2b infection. SVR_{12} rates in HCV GT2a-infected noncirrhotic subjects in Arm B were 93.9% in treatment-naive and 93.8% in treatment-experienced subjects. In contrast, SVR_{12} rates in HCV GT2b-infected subjects in Arm A were 85.7% in treatment-naïve and 56.3% in treatment-experienced subjects.

The following subgroup variables were identified by stepwise logistic regression analysis as having a statistically significant ($P < 0.10$) association with virologic failure: HCV GT2 subtype (subjects with HCV GT2a infection had lower odds of virologic failure than those with HCV GT2b infection), prior HCV treatment experience (treatment-naïve subjects had lower odds of virologic failure than treatment-experienced subjects), sex (female subjects had lower odds of virologic failure than male subjects), and RBV dose modification (subjects with RBV dose modification had lower odds of virologic failure than those without RBV dose modification).

On-treatment virologic failure rates in both treatment arms were lower in HCV GT2a-infected subjects (12-week arm: 3.4% [1/29]; 16-week arm: 6.1% [2/33]) than HCV GT2b-infected subjects (12-week arm: 15.8% [3/19]; 16-week arm: 14.3% [2/14]) in treatment-naïve, noncirrhotic subjects. On-treatment virologic failure rates in HCV GT2a-infected subjects were similar in treatment-naïve, noncirrhotic and treatment-experienced, noncirrhotic subjects. In contrast, on-treatment virologic failure rates in HCV GT2b-infected subjects were numerically higher in the treatment-experienced noncirrhotic subjects than in treatment-naïve, noncirrhotic subjects.

Agreement between SVR_{12} and SVR_{24} was 100% among all subjects in Arm B. Among the 62 subjects who achieved SVR_{12} in Arm A, 1 subject (1.6%) relapsed between Post-Treatment Week 12 and Post-Treatment Week 24. No subject who achieved SVR_{24} relapsed between Post-Treatment Week 24 and the Final Post-Treatment Visit or Post-Treatment Week 48.

A rapid (within the first week) decrease in mean HCV RNA levels was observed in noncirrhotic subjects during treatment. Rates for RVR and EOTR in all noncirrhotic subjects in both treatment arms were approximately 90% and 81%, respectively. The SVR_4 rate in all noncirrhotic subjects was 81.4% in Arm B and 76.5% in Arm A. These early responses reflected the rapid onset of virologic responses to the 2-DAA + RBV in this subpopulation.

Among noncirrhotic and cirrhotic subjects combined with ALT > ULN at baseline, treatment with the 2-DAA + RBV regimen led to normalization of ALT in 88.1% of subjects in Arm A and 89.2% of subjects in Arm B.

Summary/Conclusions (Continued)

Resistance Results:

Resistance analyses included 6 HCV GT2a- and 15 HCV GT2b-infected subjects in the 12-week arm, and 3 HCV GT2a- and 11 HCV GT2b-infected subjects in the 16-week arm who experienced virologic failure (due to on-treatment virologic failure or post-treatment relapse) and these 35 subjects were included in the PVF population. Three HCV GT2a- and 2 HCV GT2b-infected subjects who discontinued treatment early were included in the non-PVF population.

Baseline sequencing was conducted on all available samples in the study. Pre-existing resistance-associated variants in NS3 were rare in both HCV GT2a- and HCV GT2b infected samples at baseline. Amino acid position 31 in NS5A is polymorphic in HCV GT2 with prevalence of both methionine and leucine; the majority (92%, 98/106) of the HCV GT2a-infected subjects in this study had methionine at amino position 31 in NS5A, whereas 76% (48/63) and 22% (14/63) of the HCV GT2b-infected subjects had methionine and leucine, respectively, at amino acid position 31. NS5A variants T24A/S in HCV GT2a- and L28F in HCV GT2b-infected subjects were observed in 10% – 11% of the subjects at baseline. Baseline polymorphisms in NS3 or NS5A in HCV GT2a- or GT2b infected subjects did not have a significant impact on treatment outcome.

Among the 9 HCV GT2a-infected subjects in the 12-week and 16-week arms who experienced on-treatment virologic failure, D168 variants in NS3, and T24A, F28S, L31I/V, or C92S in NS5A were observed at the time of failure. Among the 26 HCV GT2b-infected subjects who experienced virologic failure, the pattern of treatment-emergent variants in NS3 and NS5A was similar across both Arms of the study. D168 variants in NS3 were observed in 24 of the 26 subjects who experienced virologic failure. NS5A variants L28F, L/M31I/V, C92S/T/Y, or Y93H were observed at the time of failure in the 26 HCV GT2b-infected virologic failure subjects.

Among the 3 HCV GT2a- and 2 HCV GT2b-infected subjects in the non-PVF population, at the time of treatment discontinuation (between Days 3 and 9), resistance-associated variants were not observed in NS3; however, all 5 subjects had resistance-associated variants at amino acid positions 24, 28, 31 or 93 in NS5A. This analysis indicates that early discontinuation of this treatment regimen may result in the emergence of resistance associated variants in NS5A.

Persistence analysis of treatment-emergent variants indicated that viral populations with 1 or more variants in NS3 in HCV GT2a-infected subjects declined through Post-Treatment Week 24 (80% [4/5]) and Post-Treatment Week 48 (40% [2/5]). Viral populations with 1 or more variants in NS3 in HCV GT2b-infected subjects declined through Post-Treatment Week 24 (78% [18/23]) and Post-Treatment Week 48 (33% [7/21]). Treatment-emergent resistance-associated variants in NS5A in HCV GT2a- and HCV GT2b-infected subjects remained detectable through Post-Treatment Week 48.

Patient-Reported Outcomes Results:

In noncirrhotic and cirrhotic subjects, the longer duration of treatment in Arm B (16 weeks) did not consistently impact HRQoL at the end of treatment or the end of the study, compared to HRQoL at end of treatment or the end of the study, respectively, in Arm A (12 weeks). The findings were less conclusive among cirrhotic subjects due to the small sample size in this group.

Pharmacokinetic Results:

Based on geometric mean C_{trough} values, subjects with compensated cirrhosis showed 74% and 33% higher ABT-450 and ritonavir exposures, respectively, while ABT-267 and RBV exposures were approximately 30% lower compared to the noncirrhotic subjects.

Summary/Conclusions (Continued)

Safety Results:

The safety population included all randomized subjects who received at least 1dose of study drug (N = 171). The majority of subjects experienced at least 1 TEAE during the Treatment Period (noncirrhotic subjects: 85.0% [136/160]; cirrhotic subjects: 63.6% [7/11]) with similar percentages of subjects experiencing a TEAE in each treatment arm (noncirrhotic subjects: 82.5% [66/80] in Arm A, 87.5% [70/80] in Arm B; cirrhotic subjects: 60.0% [3/5] in Arm A, 66.7% [4/6] in Arm B). Most subjects experienced TEAEs assessed with a maximum severity of grade 1 or 2 (> 80% of subjects in either treatment arm). Few noncirrhotic subjects experienced a TEAE that was assessed with a maximum severity of grade 3 (no subject in Arm A, 3.8% [3/80] of subjects in Arm B). All grade 3 TEAEs (uveitis, bronchopneumonia, and incisional hernia) were considered by the investigator to have no reasonable possibility of being related to study drugs. No cirrhotic subject experienced a TEAE with a severity of grade 3. No subject in the study experienced a TEAE assessed with a maximum severity higher than grade 3.

Serious TEAEs occurred in 3 subjects in the study (bronchopneumonia, alcoholic gastritis, and incisional hernia [elective]), all of whom were noncirrhotic. Each of the serious TEAEs occurred in subjects in Arm B, and each of the affected subjects had a relevant, predisposing medical history. The onset of each of the 3 serious TEAEs occurred within the first 12 weeks of the Treatment Period and therefore, these TEAEs were not related to the longer duration of treatment in Arm B (16 weeks), compared to Arm A (12 weeks). No serious TEAE was considered by the investigator to have a reasonable possibility of being related to 2-DAA. No subject in Arm A and 1 noncirrhotic subject in Arm B experienced a nonserious TEAE that led to interruption of study drugs; in the subject in Arm B, grade 1 nausea led to interruption of study drugs for 1 day (Day 3). No subject in the study experienced a TEAE that led to premature discontinuation of study drugs, and no deaths were reported.

TEAEs reported in at least 5% of noncirrhotic subjects in the treatment arms combined were anemia, blood bilirubin increased, nasopharyngitis, headache, pruritus, malaise, reticulocyte count increased, hemoglobin decreased, cough, nausea, fatigue, and rash. These AEs were consistent with the known safety profile for RBV. Pruritus has been identified as an ADR for the 2-DAA regimen and was reported in 10.0% of subjects in the treatment arms combined in this study. No specific TEAE (preferred term) occurred in more than 1 cirrhotic subject. There was no statistically significant difference between Arm A and Arm B in the overall incidences of TEAEs, the incidences of any preferred term, or the incidences of TEAEs within any of the SOCs among noncirrhotic or cirrhotic subjects.

Peripheral edema has been identified as an ADR for the 2-DAA regimen in Japanese subjects and has been associated with use and dose of concomitant CCBs. The incidences of edema-related TEAEs in noncirrhotic subjects in the treatment arms combined were 3.1% (5/160) for peripheral edema and 0.6% (1/160) for edema; no noncirrhotic subject experienced a TEAE of face edema, fluid retention, or pulmonary edema. All edema-related TEAEs were grade 1 in severity, and no edema-related TEAE was serious or led to interruption of study drugs. Of the 6 noncirrhotic subjects who experienced an edema-related TEAE, 4 were taking a concomitant CCB and 2 were not taking a concomitant CCB. Among 8 subjects who used a concomitant CCB and received the lowest CCB dose, no subject experienced an edema-related TEAE. Among 28 subjects who used a concomitant CCB and did not receive the lowest CCB dose, 14.3% (4/28) experienced an edema-related TEAE (Arm A: 16.7% [3/18]; Arm B: 10.0% [1/10]).

Summary/Conclusions (Continued)

Safety Results (Continued):

In noncirrhotic subjects, a TEAE that led to RBV dose modification (anemia, hemoglobin decreased, creatinine renal clearance decreased, or eGFR decreased) was reported in 9.4% (15/160) of subjects and occurred in a similar percentage of subjects in both treatment arms (Arm A: 10.0% [8/80]; Arm B: 8.8% [7/80]). In cirrhotic subjects, a TEAE led to RBV dose modification in 1 of 5 (20%) subjects in Arm A (grade 2 hemoglobin decreased) and 1 of 6 (16.7%) subjects in Arm B (grade 1 anemia). All TEAEs that led to RBV dose modification in noncirrhotic or cirrhotic subjects were grade 1 or 2 in severity.

Predefined TEAEs of special interest were hepatotoxicity-, bilirubin-, anemia-, and rash-related events, and were evaluated with SMQs and CMQs. Other SMQs and CMQs were used to evaluate additional pre-selected events related to acute renal failure, severe cutaneous adverse reactions, photosensitivity, rhabdomyolysis/myopathy, gallbladder-related disorders, and abuse liability. TEAEs of special interest and the additional pre-selected TEAEs were chosen based on preclinical or clinical findings in previous 2-DAA studies or safety issues identified for other therapeutic agents for HCV.

One subject was identified with the SMQ for hepatotoxicity-related events as having experienced a hepatoxicity-related TEAE (hepatic steatosis). The subject was noncirrhotic and randomized to Arm A, had a medical history of "fat disorder" and hepatic and renal cysts, and experienced grade 1, nonserious hepatic steatosis beginning on Post-Treatment Day 29. This TEAE was considered by the investigator to have no reasonable possibility of being related to 2-DAA. No subject was identified as having experienced a bilirubin-related TEAE in the study.

Anemia and hemoglobin decreased are known adverse effects of RBV administration and therefore, these TEAEs were expected. Among noncirrhotic subjects in Arm A and Arm B combined, 29.4% (47/160) of subjects were identified as having a TEAE within the SMQ for anemia-related events, with similar proportions in Arm A (27.5% [22/80]) and Arm B (31.3% [25/80]). The most common event identified was anemia (Arm A: 20.0%; Arm B: 25.0%). Anemia-related TEAEs were identified in 2 cirrhotic subjects: 1 of 5 (20%) subjects in Arm A and 1 of 6 (16.7%) subjects in Arm B.

Among all noncirrhotic or cirrhotic subjects, the majority of TEAEs identified with the SMQ for anemia-related events were assessed as grade 1 in severity. A grade 2 TEAE in the SMQ for anemia-related TEAEs was identified in a total of 5 subjects (3 in Arm A and 2 in Arm B) and no grade 3 or higher anemia-related TEAE was identified in any subject. Other than RBV dose modification, no action was taken as a result of a TEAE identified as anemia-related. In particular, no subject discontinued study drugs prematurely due to an identified anemia-related TEAE, and no subject received erythropoietin or a blood transfusion for management of anemia. All subjects were receiving concomitant RBV, and all TEAEs identified in the SMQ for anemia-related TEAEs were assessed by the investigator as having a reasonable possibility of being related to RBV. Approximately half of these events were also assessed by the investigator as having a reasonable possibility of being related to 2-DAA treatment.

Rash is a known adverse event related to RBV exposure and therefore, reports of rash-related TEAEs were expected. Among noncirrhotic subjects, the SMQ for rash-related events identified 23.8% (38/160) of subjects as having experienced a rash-related TEAE, with similar proportions in Arm A (22.5% [18/80]) and Arm B (25.0% [20/80]). In cirrhotic subjects, rash-related TEAEs were identified in 1 of 5 subjects in Arm A and 1 of 6 subjects in Arm B. The most common TEAEs identified as rash-related in noncirrhotic subjects were pruritus and rash. Overall, the nonspecific nature of the TEAEs of rash and their mild nature, as well as the fact that rash is a known adverse event related to RBV exposure, did not suggest a safety signal for rash-related events.

Summary/Conclusions (Continued)

Safety Results (Continued):

Among noncirrhotic subjects, the SMQ of acute renal failure-related events identified 6.9% (11/160) of subjects as having experienced an acute renal failure-related TEAE, with similar proportions in Arm A (8.8% [7/80]) and Arm B (5.0% [4/80]). In Arms A and B combined, the TEAEs identified in noncirrhotic subjects as acute renal failure-related were creatinine renal clearance decreased in 5 subjects, protein urine present in 3 subjects, proteinuria in 2 subjects, renal impairment in 2 subjects, blood creatinine increased in 1 subject, blood urea increased in 1 subject, and eGFR decreased in 1 subject. No cirrhotic subject was identified as having experienced an acute renal failure-related TEAE. Most TEAEs identified as acute renal failure-related events were transient and ended by Post-Treatment Week 4. These TEAEs were assessed with a maximum severity of grade 1, except for 1 event of eGFR decreased that was assessed with a maximum severity of grade 2. No TEAE identified as acute renal failure-related was serious. Based on the results, no safety signal for acute renal failure was identified.

No TEAEs were identified with the SMQ of "severe cutaneous adverse reactions" in noncirrhotic or cirrhotic subjects. Specifically, there were no events of erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, or DRESS.

No subject was identified with the SMQ for gallbladder-related disorders as having experienced a gallbladder-related TEAE.

Few subjects were identified as having experienced a TEAE within the CMQ for photosensitivity-related events, SMQ for rhabdomyolysis/myopathy-related events, or CMQ for abuse liability-related events. All TEAEs identified as photosensitivity-, rhabdomyolysis/myopathy-, or abuse liability-related were grade 1 or 2 in severity and nonserious, none of these TEAEs led to premature discontinuation of study drugs. One noncirrhotic subject experienced a TEAE identified as photosensitivity-related (chronic actinic dermatitis). This TEAE was assessed as grade 1 in severity and was nonserious. No subject experienced a cluster of symptoms suggestive of rhabdomyolysis/myopathy. Abuse liability-related TEAEs were identified in 3.8% of noncirrhotic subjects in the 12-week arm and 3.8% of noncirrhotic subjects in the 16-week arm. The events identified were dizziness and somnolence. Based on these results, no safety signal for photosensitivity- or rhabdomyolysis/myopathy-, or abuse liability-related TEAEs was identified.

Overall, mean changes in values for hemoglobin, hematocrit, and RBC count from baseline to the Final Treatment Visit, Post-Treatment Week 4 Visit, and Post-Treatment Week 48 Visit in noncirrhotic subjects were small in magnitude and similar in Arm A and Arm B. No subject met prespecified criteria for PCS values for hemoglobin, hematocrit, and RBC count. Grade 2 hemoglobin values were reported during treatment in 10.1% (16/159) of noncirrhotic subjects, with a similar percentage in each treatment arm (Arm A: 8.9% [7/79]; Arm B: 11.3% [9/80]). Two cirrhotic subjects experienced a grade 2 hemoglobin value during treatment (1 in each treatment arm). No grade 3 or 4 hemoglobin level occurred in any subject.

Summary/Conclusions (Continued)

Safety Results (Continued):

Analysis of chemistry parameters in noncirrhotic subjects showed post-baseline elevation of ALT to > 5 × ULN (grade 3 or higher) occurred in only a few subjects in Arm A (2.5% [2/79]) and no subject in Arm B. Post-baseline elevation of total bilirubin to > 3 × ULN (grade 3 or higher) occurred in noncirrhotic subjects in both Arm A (5.1% [4/79]) and Arm B (2.5% [2/80]). No subject experienced a grade 4 liver function test value. No cirrhotic subject experienced a post-baseline ALT, AST, or total bilirubin value of grade 3 or higher during treatment. All grade 3 liver function test values occurred during Weeks 1 and 2 of study treatment, except for a grade 3 total bilirubin value during Week 10 in 1 noncirrhotic subject in Arm B. Mean decreases from baseline in ALT, AST, and GGT values were observed at the Final Treatment, Post-Treatment Week 4, and Post-Treatment Week 48 Visits, and were similar in Arm A and Arm B. One subject in Arm A met the biochemical criteria for Hy's law and was evaluated by the expert hepatic panel, but the panel concluded that the subject did not meet potential Hy's law criteria.

No clinically meaningful changes from baseline or differences between Arm A and Arm B were observed in urinalysis results, vital signs, or ECG findings.

Conclusions:

The 2-DAA + RBV regimen achieved SVR_{12} rates of 91.5% with 16 weeks of treatment and 75.0% with 12 weeks of treatment in the primary efficacy population (noncirrhotic, treatment-naïve subjects) in this study in HCV GT2-infected, Japanese adults. The SVR_{12} rate demonstrated superiority to a clinically relevant threshold (based on historical SVR rates for pegIFN/RBV treated subjects in a similar population) for 16 weeks of treatment arm but not 12 weeks of treatment. Similarly, SVR_{12} rates among noncirrhotic treatment experienced subjects were higher with 16 weeks of treatment (75.8%) than with 12 weeks (68.8%), but SVR_{12} rates were lower in treatment-experienced subjects than in treatment-naïve subjects. On-treatment virologic failure rates were similar between the treatment arms, but relapse by Post-Treatment Week 12 occurred only with 12 weeks of treatment, suggesting the longer treatment duration of 16 weeks is necessary to improve SVR rates. Among subjects who achieved SVR_{12}, 1 subject in the 12-week arm and no subject in the 16-week arm relapsed between Post-Treatment Week 12 and Post-Treatment Week 24, and no subject relapsed between Post-Treatment Week 24 and Post-Treatment Week 48.

Regardless of subpopulation or treatment duration, SVR_{12} rates were higher in HCV GT2a-infected subjects than in HCV GT2b-infected subjects. Among all subjects (noncirrhotic and cirrhotic subjects) with HCV GT2a infection in the 16-week arm, the SVR_{12} rate was 92.2%. Among all noncirrhotic subjects with HCV GT2a infection in the 16-week arm, SVR_{12} rates were 93.9% in treatment-naive and 93.8% in treatment experienced subjects.

The 2-DAA + RBV regimen was generally well-tolerated in HCV GT2-infected Japanese subjects, with no subject discontinuing study drugs due to a TEAE. Anemia and pruritus are generally noted with RBV administration and were reported in > 10% of all noncirrhotic subjects, but overall were mild to moderate in severity and clinically manageable. TEAEs reported in at least 5% of noncirrhotic subjects in the treatment arms combined were anemia, blood bilirubin increased, nasopharyngitis, headache, pruritus, malaise, reticulocyte count increased, hemoglobin decreased, cough, nausea, fatigue, and rash. In cirrhotic subjects, no specific TEAE occurred in > 1 subject.

Summary/Conclusions (Continued)

Conclusions (Continued):

TEAEs reported in this study were generally grade 1 or 2 in severity, and the nature and incidences of TEAEs were generally consistent with the safety profile for the 2 DAA + RBV regimen established in other studies of this regimen. No clinically relevant difference in safety profile was observed when subjects received 12 or 16 weeks of treatment with 2-DAA + RBV. No new safety signal associated with 2-DAA was identified in the study. TEAEs reported in at least 5% of noncirrhotic subjects were consistent with the known safety profile for RBV.