2.0   Synopsis

AbbVie GK	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: paritaprevir/ritonavir/ombitasvir (ABT-450/r/ABT-267)	**Volume:** **Page:**	
Name of Active Ingredient: ABT-450: (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 ritonavir: 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*)] ABT-267: 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		
Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) in Treatment-Naïve and Treatment-Experienced Japanese Adults with Subgenotype 1b Chronic Hepatitis C Virus (HCV) Infection With and Without Compensated Cirrhosis (GIFT I)		
Coordinating Investigator: Ken Sato, MD, PhD		
Study Sites: A total of 53 investigative sites in Japan.		
Publications: 2 publications		

Studied Period (Years):
    First Subject First Visit: 25 December 2013
    Last Subject Last Visit: 01 October 2015
	Phase of Development: 3	

Objectives:

The primary objectives of this study were to compare the SVR_{12} rate (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 of treatment with ABT-450/r/ABT-267 to a clinically relevant threshold, based on the historical SVR rate of telaprevir + pegylated interferon/ribavirin (pegIFN/RBV) therapy in treatment-naïve, noncirrhotic, HCV genotype 1b (GT1b)-infected Japanese subjects who were eligible for IFN-based therapy and had a high baseline viral load and to assess the safety of the DAA combination regimen administered for 12 weeks versus placebo in noncirrhotic, HCV GT1b-infected Japanese subjects.

The secondary objectives of this study were to assess the effect of ABT-450/r/ABT-267 on HCV RNA levels as measured by on-treatment virologic failure and relapse, and SVR_{12} rates within different subpopulations.

Methodology:

This was a Phase 3, multicenter study evaluating ABT-450/r/ABT-267 in HCV GT1b-infected, treatment-naïve and treatment-experienced (prior IFN-based therapy [IFN alpha, IFN beta, or pegIFN] with or without RBV) Japanese adults without cirrhosis or with compensated cirrhosis. The study consisted of 2 substudies: Substudy 1 enrolled noncirrhotic subjects and consisted of a randomized, double-blind (DB), placebo-controlled design and Substudy 2 enrolled subjects with compensated cirrhosis and consisted of an open label (OL), single-arm design.

Substudy 1

Subjects were randomized to Arm A (DB ABT-450/r/ABT-267 150 mg/100 mg/25 mg once daily [2-DAA]) or Arm B (DB placebo once daily) in a 2:1 ratio in Substudy 1. Subjects randomized to Arm B received OL 2-DAA after the end of the DB Treatment Period:

- Arm A: DB ABT-450/r/ABT-267 150 mg/100 mg/25 mg once daily (2-DAA) for 12 weeks;
- Arm B: DB placebo once daily for 2-DAA for 12 weeks, followed by OL 2-DAA for 12 weeks.

For subjects enrolling in Substudy 1, the duration of the study was up to 72 weeks (not including a screening period of up to 35 days and any delay which occurred for electronic Case Report Form [eCRF] data entry between the end of the DB Treatment Period and the beginning of the OL period for subjects who received placebo) consisting of 3 periods: the DB Treatment Period (Arms A and B), the OL Treatment Period (for subjects enrolled into Arm B), and the Post-Treatment Period (for all subjects who received active study drugs).

The randomization for Substudy 1 was stratified by prior HCV medication history (treatment-naïve, treatment-experienced with an IFN-based therapy). The randomization for treatment-experienced subjects was also stratified by type of response to previous IFN-based treatment (nonresponder, relapser, intolerant to IFN-based therapy). The randomization for treatment-naïve subjects was also stratified by viral load (low versus high) and high viral load subjects were further stratified by eligibility for IFN-based therapy (eligible, ineligible). Low viral load was defined as HCV RNA < 100,000 IU/mL and high viral load was defined as HCV RNA 100,000 IU/mL.

Among treatment-experienced subjects, approximately 30 nonresponders, approximately 30 relapsers, and approximately 30 subjects intolerant to IFN-based therapy were to be randomized. Among the treatment-naïve subjects, approximately 150 subjects with high viral load and eligible for IFN-based therapy, approximately 30 subjects ineligible for IFN based therapy, and approximately 5 subjects with low viral load were to be randomized.

Methodology (Continued):

Substudy 2

Subjects with compensated cirrhosis were enrolled in Substudy 2 (Arm C) and received OL active treatment.

- Arm C: OL 2-DAA for 12 weeks.

For subjects enrolling in Substudy 2, the duration of the study was to be 60 weeks (not including a screening period of up to 35 days) consisting of 2 periods: the OL Treatment Period and the Post-Treatment Period (for all subjects who received active study drugs).

All subjects administered active study drugs in Substudy 1 or Substudy 2 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 outcomes (PROs).

Number of Subjects (Planned and Analyzed):

Approximately 312 subjects were planned to be randomized or enrolled across the 2 substudies. Approximately 275 subjects (approximately 185 treatment-naïve subjects and approximately 90 treatment-experienced subjects) were planned to be randomized in Substudy 1 and approximately 37 subjects were planned to be enrolled in Arm C (Substudy 2).

A total of 363 subjects were randomized or enrolled across the 2 substudies. In Substudy 1, 321 subjects (207 treatment-naïve and 114 treatment-experienced subjects) were randomized and received at least 1 dose of study drug. In Substudy 2, 42 subjects (9 treatment-naïve and 33 treatment-experienced subjects) were enrolled and received at least 1 dose of study drug.

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 GT1b infection prior to study enrollment, 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 pregnancy test results at screening and baseline, were using at least 1 effective method of birth control at the time of screening, and agreed to use 2 effective forms of birth control from Study Day 1 through 4 weeks after stopping study drug. Males were surgically sterile or practicing 2 effective methods of birth control from Study Day 1 through 4 weeks 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

Diagnosis and Main Criteria for Inclusion (Continued):

- 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.

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, CT scan, or 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 HBV or 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

Diagnosis and Main Criteria for Inclusion (Continued):

- An estimated Glomerular Filtration Rate (eGFRj) < 50 mL/min/1.73 m^2, as estimated by the 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 < 90,000 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 < 60,000 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
For Substudy 1 DB (Arms A and B) and Substudy 2 OL (Arm C) Treatment Periods					
ABT-450/ ritonavir/ ABT-267	AbbVie	Oral	Tablet	75/50/12.5 mg	13-004118
ABT-450/ ritonavir/ ABT-267 placebo	AbbVie	Oral	Tablet	0 mg	13-003102
For Substudy 1 OL Treatment Period (Arm B)					
ABT-450/ ritonavir/ ABT-267	AbbVie	Oral	Tablet	75/50/12.5 mg	13-004118

Duration of Treatment:

Subjects received 2-DAA or placebo for 12 weeks.

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

Reference therapy was placebo, as described above.

Criteria for Evaluation

Efficacy:

The primary endpoint was:

- SVR_{12}: Among noncirrhotic treatment-naïve subjects who were eligible for IFN-based therapy and who had high viral load at baseline (HCV RNA 100,000 IU/mL) (the primary efficacy population), superiority of Arm A to a clinically relevant threshold; lower bound of 95% confidence interval (LCB) had to exceed 63% to achieve superiority.

Criteria for Evaluation (Continued)

Efficacy (Continued):

Secondary efficacy endpoints assessed for subjects in Arms A and C were:

- On-treatment virologic failure, defined as the occurrence of at least one of the following:
  - confirmed HCV RNA the lower limit of quantitation (LLOQ) (defined as 2 consecutive HCV RNA measurements LLOQ) at any point during treatment after HCV RNA < LLOQ, or
  - confirmed increase from nadir in HCV RNA (defined as 2 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: 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 and with HCV RNA < LLOQ at the Final Treatment Visit and at least one post treatment HCV RNA value.
- SVR_{12} rate within the following subpopulations:
  - Noncirrhotic treatment-naïve subjects with low viral load.
  - Noncirrhotic treatment-naïve subjects who are ineligible for IFN-based therapy.
  - Noncirrhotic treatment-experienced subjects who relapsed after prior IFN-based therapy.
  - Noncirrhotic treatment-experienced subjects who were nonresponders to prior IFN-based therapy.
  - Noncirrhotic treatment-experienced subjects who were intolerant to IFN-based therapy.
  - Subjects with compensated cirrhosis.

Resistance:

For all subjects receiving active 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, and ABT-267 were tabulated and summarized.

Criteria for Evaluation (Continued)

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. Safety was summarized separately for Substudy 1 and Substudy 2.

Statistical Methods

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

The primary analysis occurred after subjects who were initially assigned to receive active study drugs (either DB treatment in Substudy 1 or OL treatment in Substudy 2) had completed the Post-Treatment Week 12 Visit or prematurely discontinued study drugs, and subjects who were initially randomized to receive placebo (DB treatment in Substudy 1) had completed 12 weeks of OL active study drug treatment in the OL Treatment Period or prematurely discontinued study drugs. A follow-up analysis occurred after subjects who were initially assigned to receive 2-DAA had completed the Post-Treatment Week 24 Visit or prematurely discontinued the study and subjects who were initially randomized to placebo had completed the Post-Treatment Week 12 Visit or prematurely discontinued from the study. 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 lower limit of quantification (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.

Primary Endpoint

To test the hypothesis that the percentage of treatment-naïve, noncirrhotic, HCV GT1b-infected subjects eligible for IFN-based therapy, with high baseline viral load and treated with 2-DAA who achieve SVR_{12} is superior to a clinically acceptable threshold (based on the historical SVR rate for the corresponding population treated with telaprevir + pegIFN/RBV), the percentage of subjects with SVR_{12} was calculated with a 2-sided 95% confidence interval (CI). The primary hypothesis was tested on subjects within the primary endpoint population who were randomized to active study drug (Arm A). The 95% CI was calculated using the normal approximation to the binomial distribution. The LCB must have been greater than 63% in order for the regimen to be considered superior to the clinically acceptable threshold in the population of treatment-naïve HCV GT1b-infected subjects with high viral load, eligible to an IFN-containing therapy.

Secondary Endpoints

The number and percentage of subjects with virologic failure, the number and percentage of subjects with relapse and the number and percentage of subjects achieving SVR_{12} within each specified subpopulation was summarized for Arm A and Arm C, along with 95% CIs using the Wilson method.

Statistical Methods (Continued)

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,

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, ABT-267, and ritonavir were tabulated for each subject and group.

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. In Substudy 1, pairwise comparisons of the percentages of subjects with TEAEs were made. 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.

Summary/Conclusions

Efficacy Results:

Noncirrhotic Subjects – Substudy 1

The SVR_{12} rate was 94.6% (106/112) in the primary efficacy population (95% CI: 90.5% to 98.8%). The LCB was above the predefined superiority threshold (63%). Therefore, the primary endpoint was achieved, and the 2-DAA regimen demonstrated superiority to the clinically relevant threshold based on the historical SVR_{12} rate with telaprevir and pegIFN/RBV in a similar population.

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. Specifically, when subjects who prematurely discontinued study drug with no on-treatment virologic failure or who were missing follow-up data in the SVR_{12} window are excluded, an SVR_{12} rate of 97.2% (106/109) is observed in the primary efficacy population.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Noncirrhotic Subjects – Substudy 1 (Continued)

SVR_{12} rates were high after double-blind (DB) treatment with 2-DAA in noncirrhotic subjects in all noncirrhotic subjects (94.9%), and in the subpopulations of noncirrhotic subjects who were treatment-naïve (94.2%) or treatment-experienced (96.1%). SVR_{12} rates were also high after open-label (OL) treatment with 2-DAA in noncirrhotic subjects who were randomized to receive DB placebo and subsequently receive OL 2-DAA for 12 weeks among all subjects (98.1%) and in the subpopulations of treatment-naïve (98.5%) or treatment-experienced (97.4%) subjects. The SVR_{12} rate with 2-DAA was 96.0% among all noncirrhotic subjects who received DB or OL 2-DAA combined. SVR_{12} rates after DB or OL treatment with 2-DAA were > 90% in all protocol-specified subpopulations of noncirrhotic subjects, which were treatment-naïve noncirrhotic subjects with either low baseline viral load or considered IFN-ineligible, and treatment-experienced noncirrhotic subjects who were prior relapsers, IFN-intolerant, or nonresponders to IFN-based therapy. Many of these subpopulations would historically be considered difficult to treat with IFN-based therapy, or were ineligible for IFN-based therapy and therefore had limited treatment options.

On-treatment virologic failure due to rebound after 2-DAA treatment occurred in 1 (0.5%) noncirrhotic subject who received DB 2-DAA and 1 (0.9%) noncirrhotic subject who received OL 2-DAA. Relapse by Post-Treatment Week 12 in noncirrhotic subjects occurred in 5 (2.4%) subjects who received DB 2-DAA and 1 (1.0%) subject who received OL 2-DAA. The other reason for failure to achieve SVR_{12} in noncirrhotic subjects was premature discontinuation of study drug in 5 (2.3%) subjects who received DB 2-DAA and no subject who received OL 2-DAA. No noncirrhotic subject experienced failure to suppress HCV RNA.

All but 1 noncirrhotic subject who achieved SVR_{12} also achieved SVR_{24}. No noncirrhotic subject in the study who achieved SVR_{24} relapsed between Post-Treatment Week 24 and the Post-Treatment Week 48 or Final Post-Treatment Visit. These observations demonstrated a maintenance of virologic response from 12 to 48 weeks after completion of 2-DAA treatment.

High RVR rates in subjects who received DB 2-DAA (96.7%) or OL 2-DAA (99.1%) reflected the rapid onset of virologic responses in this population.

The 2-DAA regimen also led to normalization of ALT in a statistically significantly higher percentage of noncirrhotic subjects who received DB 2-DAA than in those who received DB placebo (94.3% versus 18.9%, respectively, ITT population).

Cirrhotic Subjects – Substudy 2

SVR_{12} rates were high in all cirrhotic subjects (90.5% [38/42]) and in the subpopulations of treatment-naïve (100% [9/9]) and treatment-experienced (87.9% [29/33]) cirrhotic subjects. These subjects would historically be considered difficult to treat with IFN-based therapy due to the presence of cirrhosis, and most of these subjects would also be considered difficult to treat because they were not cured with prior IFN-based therapy.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

<u>**Cirrhotic Subjects – Substudy 2 (Continued)**</u>

On-treatment virologic failure due to rebound occurred in 1 (2.4%) cirrhotic subject and relapse by Post-Treatment Week 12 occurred in 2 (5.0%) cirrhotic subjects; all 3 of these subjects were treatment-experienced. The other reason for failure to achieve SVR_{12} among cirrhotic subjects was missing SVR_{12} data for 1 subject who experienced a fatal, non-treatment-emergent SAE. This fatal SAE occurred 76 days after the last dose of study drugs and prior to Post-Treatment Week 12 and was considered to have no reasonable possibility of being related to study drugs. No cirrhotic subject experienced failure to suppress HCV RNA or failure to achieve SVR_{12} due to premature discontinuation of study drugs.

All cirrhotic subjects who achieved SVR_{12} also achieved SVR_{24}. No cirrhotic subject in the study who achieved SVR_{24} relapsed between Post-Treatment Week 24 and the Post-Treatment Week 48 or Final Post-Treatment Visit. These observations demonstrated a maintenance of virologic response from 12 to 48 weeks after completion of 2-DAA treatment.

High RVR rates in cirrhotic subjects (92.9%) reflected the rapid onset of virologic responses to 2-DAA in this population.

Resistance Results:

Resistance analyses included 12 subjects in Arms A, B, and C who did not achieve SVR_{12} due to virologic failure (7 subjects in Arm A, 2 subjects in Arm B and 3 subjects in Arm C). The resistance-associated variants at the time of failure in subjects in the PVF population were: D168A and D168V, either alone or in combination with Y56H in NS3; and L31F and Y93H (either alone or in combination with L28M, R30Q, L31M/V or P58S) in NS5A. Treatment-emergent variants were similar across the noncirrhotic and cirrhotic arms of the study. Variants in NS3 in HCV GT1b-infected subjects declined through Post-Treatment Week 24 (6/12, 50%) and Post-Treatment Week 48 (2/11, 18%), while pre-existing and treatment-emergent variants in NS5A remained detectable through Post-Treatment Week 48.

Polymorphisms in NS3 at amino acid positions that have been associated with decreased activity against some members of the NS3 protease inhibitor class were observed in 62.7% (220/351) of the baseline samples. However, variants conferring resistance to ABT-450 in NS3 were not detected in any baseline sample, and there was no association between the presence of polymorphisms at baseline and treatment outcome. Polymorphisms in NS5A at amino acid positions that have been associated with decreased activity of members of the NS5A inhibitor class were observed in 67.2% (240/357) of the baseline samples. Of these, the prevalences of variants L31F and Y93H/S were 0.6% and 14.0%, respectively. Polymorphisms in NS5A at amino acid positions 28, 30, 31, 54, 58, 62 or 92 at baseline had no impact on treatment outcome. Although the presence of Y93H/S variants at baseline was associated with a numerically lower SVR_{12} rate in subjects with these polymorphisms, the overall SVR_{12} rate was high (95.3% [346/363]) for noncirrhotic subjects in Arm A (DB 2-DAA) and Arm B (OL 2-DAA) and cirrhotic subjects in Substudy 2 Arm C (OL 2-DAA) combined.

Summary/Conclusions (Continued)

Patient-Reported Outcomes Results:

In noncirrhotic subjects, improvement in HRQoL over baseline in subjects who received 2-DAA was observed in the EQ-5D-5L VAS score (but not in all other measures) at 4 weeks after completion of study treatment, and the improvement from baseline in the EQ-5D-5L VAS was similar at 48 weeks after completion of study treatment. With the exception of EQ-5D-5L Health Index score in treatment-experienced noncirrhotic subjects, the difference between DB 2-DAA and DB placebo in mean change from baseline to the Final Treatment Visit was not statistically significant.

In cirrhotic subjects, improvement in HRQoL over baseline was observed in some measures (but not in all measures) at the end of study treatment and at 4 weeks after completion of study treatment. Compared to 4 weeks after completion of study treatment, the improvement from baseline at 48 weeks after completion of study treatment was similar in the HCV-PRO Total score and increased in the EQ-5D-5L VAS.

Pharmacokinetic Results:

Based on geometric mean C_{trough} values, subjects with compensated cirrhosis showed 116% and 48% higher ABT-450 and ritonavir exposures, respectively, compared to noncirrhotic subjects, while ABT-267 exposures were comparable between noncirrhotic and cirrhotic subjects.

Safety Results:

Noncirrhotic Subjects – Substudy 1

The 2-DAA regimen was generally well-tolerated in noncirrhotic subjects. TEAEs were reported for 69.3% of subjects in the 2-DAA arm and 56.6% of subjects in the placebo arm during the DB Treatment Period, and the difference between the treatment arms was statistically significant. During the OL Treatment Period of Substudy 1, 64.2% of subjects who received 2-DAA reported TEAEs. For most subjects, the maximum severity of TEAEs was assessed as grade 1 (DB treatment: 38.6% 2-DAA; 31.1% placebo; OL treatment: 39.6% 2-DAA) or grade 2 (DB treatment: 25.1% 2-DAA, 23.6% placebo; OL treatment: 22.6% 2-DAA). Few subjects experienced TEAEs that were assessed with a maximum severity of grade 3 (DB treatment: 5.6% 2-DAA; 1.9% placebo; OL treatment: 1.9% 2-DAA). No noncirrhotic subject experienced a TEAE assessed with a severity of grade 4 or 5. The incidence of TEAEs that resulted in discontinuation of study drugs was low in noncirrhotic subjects (2 [0.9%] subjects with DB 2-DAA [grade 3 hypotension, grade 3 anuria] and no subject with DB placebo or OL 2-DAA). No deaths were reported among noncirrhotic subjects.

Treatment-emergent AEs reported in at least 5% of noncirrhotic subjects in either treatment group were nasopharyngitis (16.7% 2-DAA, 13.2% placebo), headache (8.8% 2-DAA, 9.4% placebo), and peripheral edema (5.1% 2-DAA, 0% placebo). The difference between the 2-DAA and placebo treatment arms was statistically significant for the incidence of peripheral edema. During the OL Treatment Period, TEAEs reported in at least 5% of noncirrhotic subjects were nasopharyngitis (7.5%) and headache (6.6%).

All noncirrhotic subjects who experienced peripheral edema were also taking concomitant CCBs. Because CCBs have a known DDI with ritonavir, concomitant administration of 2-DAA with CCBs may result in increased plasma levels of CCBs and thereby, increase or prolong their therapeutic and adverse effects (e.g., potential for edema-related TEAEs).

Summary/Conclusions (Continued)

Safety Results (Continued):

Noncirrhotic Subjects – Substudy 1 (Continued)

No specific safety concerns related to sex, age, BMI, baseline fibrosis stage, prior HCV medication history, baseline platelet count, or baseline hepatoprotective drug use were identified in noncirrhotic subjects, based on analysis of data from the DB Treatment Period. Although peripheral edema occurred more frequently in noncirrhotic subjects aged 65 years than in those aged < 65 years, in female than in male subjects, and in subjects who were using hepatoprotective medications than in those who were not, these findings appeared to be primarily associated with the concomitant use of CCBs. However, sample sizes for many subgroups were small, and definitive conclusions could not be made.

The incidence of serious TEAEs was low in the 2-DAA (3.3%) and placebo (1.9%) during DB treatment and during OL treatment with 2-DAA (2.8%), and there was no clear pattern in the type of event or time of onset for serious TEAEs. Serious TEAEs led to discontinuation of study drugs in 2 subjects who were receiving DB 2-DAA (due to hypotension or anuria). Both of these subjects were taking concomitant CCBs. No other TEAEs in noncirrhotic subjects led to discontinuation of study drugs. TEAEs led to interruption of study drugs in 1 subject who was receiving DB 2-DAA (due to three grade 3, nonserious TEAEs [headache, nausea, and vomiting]) and 1 subject who was receiving DB placebo (due to grade 3, serious rectosigmoid cancer and grade 3, nonserious suture rupture).

One subject in the study was identified as having experienced a hepatotoxicity-related TEAE, based on diagnosis with a grade 3 serious TEAE of HCC; this event was considered to have no reasonable possibility of being related to study drugs.

No TEAE was identified in noncirrhotic subjects with SMQs/CMQs for bilirubin-related, gallbladder-related disorders, or severe cutaneous reactions. One TEAE (grade 2 photophobia) was identified with the CMQ for photosensitivity in a subject who received DB 2-DAA. No events of erythema multiforme, toxic epidermal necrolysis, Stevens Johnson syndrome, or phototoxicity were reported.

Anemia-related events were identified in a low percentage of noncirrhotic subjects who received 2-DAA (DB treatment: 2.3%; OL treatment: 1.9%). No actions (e.g., erythropoietin administration or transfusion) were taken because of these events.

Acute renal failure-related TEAEs were identified in 3.3% of subjects who received DB 2-DAA and no subject who received OL 2-DAA. The acute renal failure-related TEAEs identified included the serious TEAE of anuria that led to premature discontinuation of study drugs, was grade 3 in severity, but resolved after 3 days, and the nonserious, grade 3 event of renal impairment that was identified after premature discontinuation of study drugs, and resolved after about 2 weeks with medication.

No subject experienced more than 1 TEAE identified as related to rhabdomyolysis/myopathy, or a cluster of TEAEs that would be required to identify an event of rhabdomyolysis and/or myopathy. No safety signal for abuse liability was identified.

Summary/Conclusions (Continued)

Safety Results (Continued):

Noncirrhotic Subjects – Substudy 1 (Continued)

The only clinically relevant changes observed in chemistry parameters in noncirrhotic subjects were in liver function test values in subjects who received DB or OL 2-DAA. Mean decreases from baseline to end of treatment occurred in ALT, AST, and GGT with 2-DAA treatment, and during DB treatment, these decreases were statistically significantly greater in the 2-DAA arm than in the placebo arm. The differences between the 2-DAA and placebo arms reached statistical significance at the first week of study treatment, suggesting a rapid response to the 2-DAA regimen. An asymptomatic increase in indirect bilirubin was seen around the first week of DB or OL treatment with 2-DAA, consistent with the inhibition of OATP1B1 by ABT-450, with subsequent small mean changes in indirect bilirubin from baseline to the Final DB Treatment, Post-Treatment Week 4, and Post-Treatment Week 48 Visits. In the placebo arm, indirect bilirubin exhibited only small mean changes from baseline at the first week of DB treatment and from baseline to the Final DB Treatment, Post-Treatment Week 4, and Post-Treatment Week 48 Visits. The magnitude of mean changes from baseline in total, direct, and indirect bilirubin was small (< 2.5 µmol/L) and not considered to be clinically relevant. No noncirrhotic subject met the biochemical criteria for Hy's Law during DB or OL treatment.

Small improvements in platelet counts, INR, and albumin from baseline to end of treatment, in conjunction with marked reductions in liver enzyme levels, suggested a trend toward overall improvement in hepatic function in noncirrhotic subjects who received DB 2-DAA, compared to those who received placebo. The trends observed in subjects who received OL 2-DAA were comparable to those observed in subjects who received DB 2-DAA.

Cirrhotic Subjects – Substudy 2

The 2-DAA regimen was generally well-tolerated in cirrhotic subjects. Although TEAEs were reported in 73.8% of cirrhotic subjects, only 2 of these subjects experienced a TEAE with a severity of grade 3. For both of these subjects, the TEAE was grade 3 and was serious. One of these 2 subjects experienced a grade 3, serious TEAE (pulmonary edema) that was the only TEAE to lead to premature discontinuation of study drugs in a cirrhotic subject. The other subject experienced a grade 3, serious TEAE of metastases to bone. Subsequently, after completion of study treatment, this subject experienced a non-treatment-emergent, serious adverse event of lymphangiosis carcinomatosa that was not considered to have a reasonable possibility of being related to study drugs, but was fatal. Another cirrhotic subject experienced a grade 3, non-treatment-emergent, serious adverse event of HCC on the last day of study drug treatment, and the HCC progressed rapidly and led to the subject's death.

Treatment-emergent adverse events reported in at least 5% of cirrhotic subjects were nasopharyngitis (14.3%), pyrexia (9.5%), nausea (7.1%), peripheral edema (7.1%), platelet count decreased (7.1%), headache (7.1%), and eczema (7.1%). Four (9.5%) of the 42 cirrhotic subjects experienced edema-related TEAEs, and all 4 subjects were taking concomitant CCBs and therefore, may have been at increased risk for TEAEs related to DDI, such as edema. The edema-related TEAEs in cirrhotic subjects were grade 1 or 2 in severity, with the exception of the grade 3, serious TEAE of pulmonary edema.

No specific safety concerns related to subgroups were identified in cirrhotic subjects, but sample sizes for many subgroups were small, and definitive conclusions could not be made.

No cirrhotic subject was identified as having experienced a hepatotoxicity-, bilirubin-, or gallbladder-related TEAE, or as having a TEAE related to acute renal failure, rhabdomyolysis/myopathy, severe cutaneous adverse reactions, or photosensitivity.

Summary/Conclusions (Continued)

Safety Results (Continued):

Cirrhotic Subjects – Substudy 2 (Continued)

Anemia-related TEAEs were identified in 7.1% of cirrhotic subjects; all were nonserious, and all but 1 of these TEAEs were grade 1 in severity. Rash-related TEAEs were identified in 19.0% of cirrhotic subjects, but all were grade 1 or 2 in severity, nonserious, and did not result in discontinuation of study drugs. No events of erythema multiforme, toxic epidermal necrolysis, Stevens Johnson syndrome, or phototoxicity were reported in cirrhotic subjects.

In general, mean changes in hematology parameters in cirrhotic subjects were small in magnitude and not considered to be clinically relevant. These findings suggest a minimal risk for occurrence of cytopenias with the 2-DAA regimen in cirrhotic patients, in contrast to with IFN-based therapies. Notably, no cirrhotic subject had a hematology parameter value that met PCS criteria during the Treatment Period.

The only clinically relevant changes observed in chemistry parameters in cirrhotic subjects were in liver function test values. Mean decreases from baseline (toward normal values) in ALT, AST, and GGT values were apparent in cirrhotic subjects at the first week of study treatment, similar to results observed in noncirrhotic subjects who received the 2-DAA regimen. For indirect bilirubin, a mean increase from baseline was observed at Week 1, followed by small mean changes in indirect bilirubin values from baseline to the Final OL Treatment Visit and subsequent time points. Post-baseline values of grade 2 occurred in no cirrhotic subject for ALT or AST, 2 (4.8%) cirrhotic subjects for alkaline phosphatase, and 4 (9.5%) cirrhotic subjects for total bilirubin. A grade 3 liver function test result occurred in only 1 cirrhotic subject (grade 3 total bilirubin on Day 7), decreased (toward baseline value) by the end of treatment, and was not associated with a TEAE. No cirrhotic subject met the criteria for Hy's law or a subset of Temple's corollary quadrant.

Small improvements in platelet counts, INR, and albumin from baseline to end of treatment, in conjunction with marked reductions in liver enzyme and total bilirubin levels, suggested a trend toward overall improvement in hepatic function in cirrhotic subjects.

Summary/Conclusions (Continued)

Conclusions:

In HCV GT1b-infected, IFN-eligible Japanese adults without cirrhosis and with high baseline viral load, the 2-DAA regimen (ABT-450/r/ABT-267 150/100/25 mg once daily for 12 weeks) achieved a SVR_{12} rate of 94.6%, demonstrating superiority to a clinically relevant threshold based on the historical SVR_{12} rate with telaprevir plus pegIFN. The 2-DAA regimen achieved high SVR_{12} rates (> 90%) in all protocol-specified subpopulations, which were treatment-naïve noncirrhotic subjects with either low baseline viral load or considered IFN-ineligible, treatment-experienced noncirrhotic subjects who were prior relapsers, IFN-intolerant, or nonresponders to IFN-based therapy, and cirrhotic subjects. Rates of on-treatment virologic failure and post-treatment relapse were low in both noncirrhotic and cirrhotic subjects; in all but 1 subject with a virologic response at 12 weeks after completion of treatment, the response was maintained through at least 48 weeks after completion of 2-DAA treatment. The 2-DAA regimen was generally well-tolerated, with 2 (0.9%) noncirrhotic subjects who received DB treatment, no noncirrhotic subject who received OL treatment, and 1 (2.4%) cirrhotic subject (OL treatment) discontinuing the 2-DAA regimen due to a TEAE. The 2-DAA regimen was well-tolerated with respect to TEAEs such as anemia and cutaneous reactions that are generally noted with other HCV DAAs (e.g., boceprevir, telaprevir, and simeprevir). The only TEAEs that occurred in > 10% of all noncirrhotic or cirrhotic subjects who received 2-DAA was nasopharyngitis. Peripheral edema was the only TEAE that occurred at a significantly higher rate with 2-DAA than placebo in noncirrhotic subjects during DB treatment. In all cases, subjects who experienced peripheral edema were taking concomitant CCBs and may therefore have been at increased risk for TEAEs related to DDI, such as edema. 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 regimen established in the Phase 2 study in Japanese subjects (Study M12-536) and in other studies of the 2-DAA regimen.