2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-450, ritonavir, ABT-267, ABT-333		
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,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate **ritonavir:** [5S-(5R*,8R*,10R*,11R*)]-10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester **ABT-267:** Dimethyl ([(2S,5S)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate **ABT-333:** Sodium 3-(3-tert-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1)		
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) and ABT-333 in Treatment-Naïve and Treatment-Experienced, Non-Cirrhotic Asian Adults with Subgenotype 1b Chronic Hepatitis C Virus (HCV) Infection		
Coordinating Investigator: [redacted]		
Study Sites: 53 sites in China, South Korea, and Taiwan for the Post-Treatment (PT) Week 24 analysis		
Publications: 1 (abstract)		

Studied Period (Years): First Subject First Visit: 16 July 2015 Last Subject Last Visit: 18 October 2016 (PT Week 24 analysis)	**Phase of Development:** 3

Objectives:

The primary objectives of this study are to compare, among treatment-naïve subjects and among treatment-experienced subjects, the percentage of subjects achieving SVR_{12} (the percentage of subjects achieving a 12-week sustained virologic response [SVR; defined as HCV ribonucleic acid [RNA] < lower limit of quantitation {LLOQ} 12 weeks following therapy]), and the percentage of subjects achieving SVR_{24} (HCV RNA < LLOQ 24 weeks following therapy) (SVR_{24} for China only) with the combination regimen of ABT-450/r/ABT-267 and ABT-333 (hereafter, 3-DAA) to the historical SVR rate of telaprevir + pegylated interferon/ribavirin (pegIFN/RBV) therapy and to assess the safety of the 3-DAA combination regimen versus placebo for 12 weeks in HCV GT1b-infected adults without cirrhosis.

The secondary objectives are to demonstrate the effect of the 3-DAA combination regimen on HCV RNA levels during and after treatment as measured by on treatment virologic failure and post-treatment (PT) relapse, respectively.

Methodology:

This is a Phase 3, randomized, double-blind (DB), placebo-controlled, multicenter study evaluating the 3-DAA combination regimen in treatment-naïve and treatment-experienced, noncirrhotic HCV genotype (GT) 1b-infected adults. Approximately 640 HCV GT1b-infected, treatment-naïve and treatment-experienced adults were to be randomized 1:1 to Arms A and B in the DB Treatment Period.

Arm A: ABT-450/r/ABT-267 150 mg/100 mg/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) (3-DAA) for 12 weeks during the DB Treatment Period;

Arm B: Placebo for ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + placebo for ABT-333 250 mg BID for 12 weeks during the DB Treatment Period followed by 3-DAA for 12 weeks during the Open-Label (OL) Treatment Period.

Randomization was stratified by geographic region (China, South Korea, Taiwan), and subject's prior treatment experience (treatment-naïve, treatment-experienced).

The study consists of 3 periods: a 12-week DB Treatment Period, a 12-week OL Treatment Period (for subjects randomized to placebo in the DB Treatment Period [Arm B]), and a 48-week PT Period (for all subjects who received active study drugs). Subjects who received 3-DAA in the DB or OL Treatment Periods and demonstrated evidence of virologic failure were to be discontinued from 3-DAA therapy and initiate the PT Period. All subjects administered active study drugs are to be followed for 48 weeks PT to monitor for safety, HCV RNA, the emergence and/or persistence of resistant viral variants, and assessment of patient-reported outcomes (PROs [not required for Arm B during the OL and PT Periods]).

Reported herein are results of analyses of data collected through PT Week 24.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 640 subjects, including approximately 400 subjects from sites in China (200 treatment-naïve and 200 treatment-experienced subjects) and 120 subjects (80 treatment-naïve and 40 treatment-experienced subjects) each from sites in South Korea and Taiwan, respectively.

Analyzed: 650 subjects, including 410 subjects (206 treatment-naïve and 204 treatment-experienced subjects) from sites in China and 120 subjects (80 treatment-naïve and 40 treatment-experienced subjects) each from sites in South Korea and Taiwan, respectively.

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria:

1. Male or female of Chinese, South Korean, or Taiwanese descent with full Chinese, South Korean, or Taiwanese parentage between the ages of 18 and 70 years of age.
2. Chronic HCV infection prior to study enrollment.
3. HCV GT1b infection.
4. Per local standard practice, documented absence of cirrhosis.
5. Subject had never received antiviral treatment (including interferon [IFN]-based therapy [IFN {alpha, beta or pegIFN} with or without ribavirin {RBV}]) for hepatitis C infection (treatment naïve subject) or subject had documentation that they met the definition of 1 of the following categories (treatment-experienced subject).
   - Non-responder: received at least 12 weeks of IFN-based therapy (IFN [alpha, beta or pegIFN] with RBV) 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 (IFN [alpha, beta or pegIFN] with RBV) for the treatment of HCV and was undetectable at or after the end of treatment, but subsequently had detectable HCV RNA within 24 weeks of treatment follow-up.
6. Subject had plasma HCV RNA level > 10,000 IU/mL at screening.

Main Exclusion Criteria:

1. Any HCV GT other than GT1b.
2. Positive test result at screening for hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV) deoxyribonucleic acid (DNA) > LLOQ if HBsAg negative or anti-human immunodeficiency virus (HIV) antibody.
3. Any current or past clinical evidence of cirrhosis.
4. Any primary cause of liver disease other than chronic HCV-infection.

Diagnosis and Main Criteria for Inclusion (Continued):

Main Exclusion Criteria (Continued):

5. Screening laboratory analyses showing any of the following abnormal laboratory results.
   - alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN); or
   - aspartate aminotransferase (AST) > 5 × ULN;
   - estimated glomerular filtration rate (eGFR) adjusted for the Chinese population < 50 mL/min/1.73 m^2 as estimated by the Chinese-Modification of Diet in Renal Disease (C-MDRD) method, modified for the Chinese population, according to the following formula: $eGFR = 175 \times (\text{serum creatinine})^{-1.234} \times (\text{age})^{-0.179} \times (0.79 \text{ if female})$;
   - albumin < lower limit of normal (LLN);
   - prothrombin time/international normalized ratio (INR) > 1.5. Subjects with a known inherited blood disorder and INR > 1.5 could have been enrolled with permission of the AbbVie study-designated physician;
   - hemoglobin < LLN;
   - platelets < 100,000 cells/mm^3;
   - absolute neutrophil count < 1,500 cells/µL;
   - indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN.

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

Investigational Product	Manufacturer	Dosage Form/Mode of Administration	Bulk Lot Number
ABT-450/ritonavir/ ABT-267	AbbVie	75 mg/50 mg/12.5 mg tablet/oral	14-005707
ABT-450/ritonavir/ ABT-267 placebo	AbbVie	0 mg tablet/oral	14-005785
ABT-333	AbbVie	250 mg tablet/oral	14-005080
ABT-333 placebo	AbbVie	0 mg tablet/oral	14-004343

Duration of Treatment:

In the DB Treatment Period, subjects received ABT-450/r/ABT-267 and ABT-333 or matching placebos for 12 weeks. Subjects randomized to placebo (Arm B) received ABT-450/r/ABT-267 and ABT-333 for 12 weeks in the OL Treatment Period.

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

Reference therapy was placebo, as described above.

Criteria for Evaluation

Efficacy:

HCV RNA in IU/mL was assessed at all Treatment Period visits and at all PT visits.

Resistance:

The following resistance information was provided for subjects receiving active study drugs who did not achieve SVR_{12} due to virologic failure (who had 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 prototypic reference sequence;
- the amino acid variants in available post-baseline samples identified by population nucleotide sequencing and comparison to the baseline sequence;
- the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by population nucleotide sequencing and comparison to the prototypic reference sequence.

In addition, a listing of amino acid variants that emerged in isolates from at least 2 subjects was provided, and the persistence of viral resistance-associated amino acid variants was to be summarized.

Patient-Reported Outcomes:

The change in disease-specific function and well-being was assessed using the HCV Patient Reported Outcomes (HCV PRO) instrument. Health State Utility was measured using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L). General Health Related Quality of Life (HRQoL) was assessed using the Short Form 36, version 2 (SF-36V2) non-disease specific HRQoL instrument.

Pharmacokinetics:

Individual plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333, and the ABT-333 M1 metabolite were determined at each visit for subjects treated with the active regimen in the DB Treatment Period and the OL Treatment Period.

Safety:

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

Statistical Methods

All subjects who received at least 1 dose of DB study drug (active or placebo) were included in the analysis. Data collected during the DB Treatment Period were summarized for Arms A and B. Data collected during the OL Treatment Period were summarized for Arm B subjects who received at least 1 dose of active study drug during the OL Treatment Period. Post-treatment data were summarized for Arm A and Arm B subjects.

Statistical Methods (Continued)

Efficacy:

Primary Endpoints

The primary endpoints for this study were the percentages of treatment-naïve Arm A subjects and treatment-experienced Arm A subjects achieving SVR_{12} and SVR_{24} (primary endpoint for China only).

For China, in order to control the Type I error rate at 0.05, a fixed-sequence testing procedure was used to proceed through the primary efficacy endpoints for the treatment-naïve and treatment-experienced populations. That is, only if success was demonstrated for the primary endpoint of superiority of the SVR_{12} rate to the historical rate for telaprevir plus pegIFN and RBV therapy would the testing continue to the second primary endpoint of superiority of the SVR_{24} rate to the historical rate for telaprevir plus pegIFN and RBV therapy.

To test the hypothesis that the percentage of treatment-naïve HCV GT1b-infected subjects treated with 3-DAA who achieved SVR_{12}/SVR_{24} was superior to the historical SVR rate for the corresponding population treated with telaprevir plus pegIFN and RBV, the simple percentage of subjects with SVR_{12}/SVR_{24} was calculated with a 2-sided 95% confidence interval (CI), using the Wilson score method for a single proportion. The lower bound of the 95% CI (LCB) must have exceeded 84% in order for the regimen to be considered superior to the historical SVR rate in treatment-naïve HCV GT1b-infected subjects treated with telaprevir plus pegIFN and RBV.

Similarly, to test the hypothesis that the percentage of treatment-experienced HCV GT1b-infected subjects treated with 3-DAA who achieved SVR_{12}/SVR_{24} was superior to the historical SVR rate for the corresponding population treated with telaprevir plus pegIFN and RBV, the simple percentage of subjects with SVR_{12}/SVR_{24} was calculated with a 2-sided 95% CI, using the Wilson score method. The LCB must have exceeded 75% in order for the regimen to be considered superior to the historical SVR rate in treatment-experienced HCV GT1b-infected subjects treated with telaprevir plus pegIFN and RBV.

Secondary Endpoints

The number and percentage of subjects with on-treatment virologic failure, the number and percentage of subjects with relapse by PT Week 12, and the number and percentage of subjects with relapse by PT Week 24 were calculated, along with 95% CIs calculated using the Wilson score method, for Arm A treatment-naïve subjects and for Arm A treatment-experienced subjects.

As sensitivity analyses, the primary endpoints were summarized by geographic region (China, South Korea, Taiwan). As additional analyses, the secondary endpoints were also summarized by geographic region.

Resistance:

For subjects receiving study drugs who experienced virologic failure (who had HCV RNA $\geq$ 1000 IU/mL), the variants at baseline at signature resistance-associated positions identified by population nucleotide sequencing compared to the prototypic reference sequence, the amino acid variants in available postbaseline samples identified by population nucleotide sequencing compared to the baseline sequence, and the amino acid variants in available postbaseline samples at signature resistance-associated positions identified by population nucleotide sequencing compared to the prototypic reference were to be summarized.

Statistical Methods (Continued)

Patient-Reported Outcomes:

Exploratory analyses of the change in non-disease-specific HRQoL, HCV-specific function and well-being, and health state utility were measured using the SF-36v2, HCV PRO, and EQ-5D-5L instruments, respectively. SF-36v2 was analyzed by physical and mental component scores. EQ-5D-5L was analyzed by utility score and by visual analogue scale (VAS) response. Change from baseline to final DB Treatment Visit in the patient reported outcome (PRO) summary measures were summarized and compared between treatment arms using ANCOVA models with a treatment group factor and the baseline score as a covariate.

The number and percentage of subjects with a decrease that was less than the minimally important difference (MID) from baseline to the Final DB Treatment Visit for HCV-PRO total score, EQ-5D-5L health index, and SF-36v2 component summary scores were calculated for all subjects in each treatment arm. The MIDs for the HCV-PRO total score and the EQ-5D-5L health index were based on receiver operating characteristic curves anchored by SF-36v2 Mental Component Summary and SF-36v2 Physical Component Summary decreases of 5 points.

Pharmacokinetics:

Plasma concentrations of ABT-450, ABT-267, ABT-333, ABT-333 M1 metabolite, and ritonavir and time after last dose were listed for each subject in the DB Treatment Period and the OL Treatment Period of active regimen. C_{trough} was calculated by binning of the concentrations in time interval of > 22 – 26 hours for QD drugs and > 10 to 14 hours for BID drugs based on time after last dose across all visits after Week 2 for each subject. Summary statistics for concentrations in each time interval were computed by analyte and geographic region.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of subjects with treatment-emergent adverse events (TEAEs) were tabulated by primary System Organ Class (SOC) and preferred term for each treatment arm. Tabulations were also provided in which the number of subjects reporting a TEAE (preferred term) in each treatment arm was presented by severity rating (mild, moderate, or severe), severity grade (1, 2, 3, or 4), and relationship to study drugs. Comparisons of the treatment arms were performed using Fisher's exact test.

Changes from baseline in laboratory tests and vital sign measurements to each time point of collection during the DB Treatment Period were summarized by treatment group and compared between treatment groups using analysis of variance (ANOVA) with treatment group as factor.

Laboratory and vital sign values that are potentially clinically significant (PCS), according to predefined criteria, were identified, and the percentages of subjects with PCS values during the DB Treatment Period were compared between treatment groups using Fisher's exact test. Hemoglobin and liver function tests were also categorized using Common Terminology Criteria for Adverse Events (CTCAE) grades, and the percentages of subjects with CTCAE grades of at least 2 and at least 3 during the DB Treatment Period were compared between treatment groups using Fisher's exact test.

Summary/Conclusions

Efficacy Results:

SVR_{12} and SVR_{24} were achieved in 183 of 184 (99.5%) Arm A treatment-naive subjects, with the LCB above the 84% superiority threshold for each rate (refer to table below). SVR_{12} and SVR_{24} were achieved in all (100%, 141/141) Arm A treatment-experienced subjects, with the LCB above the 75% superiority threshold for each rate. Therefore, the primary SVR_{12} and SVR_{24} endpoints were achieved, and 3-DAA demonstrated superiority to the historical control rate for therapy based on telaprevir plus pegIFN and RBV, irrespective of prior treatment status.

One 3-DAA-treated subject experienced on-treatment virologic failure with concentrations of 0 ng/mL for all components of the 3-DAA regimen at all study visits. No subject relapsed during the 12 weeks after completing treatment in the DB Treatment Period.

Summary/Conclusions (Continued)

Primary Efficacy Endpoint: Virologic Response (SVR_{12}, SVR_{24}) in Arm A (ITT Population)

	Treatment-Naïve		Treatment-Experienced	
Virologic Finding	**SVR_{12}**	**SVR_{24}**	**SVR_{12}**	**SVR_{24}**
SVR, n/N (%)	183/184 (99.5)	183/184 (99.5)	141/141 (100)	141/141 (100)
95% CI[a]	97.0, 99.9	97.0, 99.9	97.4, 100.0	97.4, 100.0
Nonresponders, n/N (%)	1[b]/184 (0.5)	1[b]/184 (0.5)	0/141	0/141
Reason for nonresponse, n/N (%)				
On-treatment virologic failure	1[b]/184 (0.5)	1[b]/184 (0.5)	0/141	0/141
Rebound	0/184	0/184	0/141	0/141
Fail to suppress	1[b]/184 (0.5)	1[b]/184 (0.5)	0/141	0/141
Relapse by PT Week 12	0/183[c]	0/183[c]	0/141	0/141
Relapse by PT Week 24 after achieving SVR_{12}	NA	0/182[c,d]	NA	0/141
Premature study drug discontinuation	0/184	0/184	0/141	0/141
Missing SVR_{12}/SVR_{24} data	0/184	0/184	0/141	0/141
Other	0/184	0/184	0/141	0/141
Threshold based on historic TVR plus pegIFN and RBV-based SVR rates[e]				
	84%	84%	75%	75%

CI = confidence interval; DAA = direct-acting antiviral agent; NA = not applicable; pegIFN = pegylated interferon; PT = post-treatment; r = ritonavir; RBV = ribavirin; SVR = sustained virologic response; SVR_{12} = sustained virologic response at 12 weeks postdosing; TVR = telaprevir

a. Calculated using the Wilson score method.

b. Pharmacokinetic analysis showed that this (Chinese) subject had concentrations of 0 ng/mL for all components of the 3-DAA regimen at all study visits.

c. One (Chinese) subject had HCV-RNA ≥ LLOQ at the Final DB Treatment Period visit, and therefore, was not included in the analysis of relapse by PT Week 12. This subject did not achieve SVR_{12}, and therefore, was not included in the analysis of relapse by PT Week 24 after achieving SVR_{12}.

d. One (Korean) subject did not have HCV RNA data available during the SVR_{24} window, and therefore, was not included in the analysis of relapse by PT Week 24 after achieving SVR_{12}. No missing data imputation was performed for relapse analyses.

e. Rate for HCV GT1b-infected adults without cirrhosis.

Note: Arm A treated with 3-DAA = ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

For each geographic region, the LCBs for SVR_{12} and SVR_{24} were above the historical TVR/pegIFN/RBV SVR threshold of 84% for the treatment-naïve population and 75% for the treatment-experienced population and was also above the corresponding historical pegIFN ± RBV SVR rate for each region.

Virologic Response (SVR_{12}, SVR_{24}) in Arm A by Geographic Region (ITT Population)

	Treatment-Naïve		Treatment-Experienced	
Geographic Region	**SVR_{12}**	**SVR_{24}**	**SVR_{12}**	**SVR_{24}**
China				
SVR, n/N (%)	103[b]/104 (99.0)	103[b]/104 (99.0)	101/101 (100)	101/101 (100)
95% CI[a]	94.8, 99.8	94.8, 99.8	96.3, 100.0	96.3, 100.0
Historic geographic region-specific pegIFN ± RBV SVR rates	73.6%	73.6%	68.0%	68.0%
South Korea				
SVR, n/N (%)	40/40 (100)	40/40 (100)	20/20 (100)	20/20 (100)
95% CI[a]	91.2, 100.0	91.2, 100.0	83.9, 100.0	83.9, 100.0
Historic geographic region-specific pegIFN + RBV SVR rates	69.5%	69.5%	47.0%	47.0%
Taiwan				
SVR, n/N (%)	40/40 (100)	40/40 (100)	20/20 (100)	20/20 (100)
95% CI[a]	91.2, 100.0	91.2, 100.0	83.9, 100.0	83.9, 100.0
Historic geographic region-specific pegIFN + RBV SVR rates	79.0%	79.0%	52.0%	52.0%
Overall				
SVR, n/N (%)	183/184 (99.5)	183/184 (99.5)	141/141 (100)	141/141 (100)
95% CI[c]	98.4, 100.0	98.4, 100.0	100.0, 100.0	100.0, 100.0
Test for homogeneity across geographic regions[d]	0.679	0.679	NA	NA

CI = confidence interval; DAA = direct-acting antiviral agent; NA = not applicable; pegIFN = pegylated interferon; r = ritonavir; RBV = ribavirin; SVR = sustained virologic response; SVR_{12} = sustained virologic response at 12 weeks postdosing; SVR_{24} = sustained virologic response at 24 weeks postdosing

a. Calculated using the Wilson score method.

b. One subject was a non-responder due to failure to suppress. Pharmacokinetic analysis showed that this subject had concentrations of 0 ng/mL for all components of the 3-DAA regimen at all study visits.

c. Calculated using a geographic region-weighted proportion and variance.

d. P-value based on Pearson $\chi 2$ test.

Note: Arm A treated with 3-DAA = ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID.

Summary/Conclusions (Continued)

Resistance Results:

Baseline polymorphisms – Y56F in NS3, P58S in NS5A, and C316N in NS5B – were identified in the 1 subject in Arm A who experienced on-treatment virologic failure. At the time point closest in time after virologic failure, treatment-emergent substitution Y93H was detected in NS5A, while treatment-emergent substitutions at signature amino acid positions were not detected in NS3 or NS5B. Note that pharmacokinetic analysis showed that this subject had concentrations of 0 ng/mL for all components of the 3-DAA regimen at all study visits.

The 1 subject in Arm B who experienced relapse at PT Week 12 had baseline polymorphisms at signature amino acid positions in NS5A (Q24K, L28M, R30Q, and Y93H) and NS5B (C316N, S556G). At the time of virologic failure, treatment-emergent substitution D168V was detected in NS3, whereas there were no treatment-emergent substitutions at signature amino acid positions in NS5A or NS5B.

PRO Results:

The majority of subjects who were treated with 3-DAA did not experience decreases from baseline that exceeded the minimally important difference in their HRQoL, function, and wellbeing (per SF-36v2 Mental Component Summary, Physical Component Summary, and HCV-PRO total scores) at the end of treatment.

Pharmacokinetic Results:

ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1 exposures are comparable between Chinese, Korean, and Taiwanese noncirrhotic HCV GT1b-infected subjects, and between those who received 3-DAA during the DB Treatment Period and those who received 3-DAA during the OL Treatment Period.

Safety Results:

The incidence of TEAEs reported during the DB Treatment Period was higher in the 3-DAA treatment group compared to the placebo group (58.8% versus 49.5%). The majority of subjects who experienced TEAE(s) had mild events as their most severe events, and most TEAEs were considered not related to the 3-DAA regimen.

Summary/Conclusions (Continued)

Safety Results (Continued):

Overview of Adverse Events During the Double-Blind Treatment Period (Safety Population)

	Number (%) of Subjects							
			Geographic Region					
	All Subjects		China		South Korea		Taiwan	
Type of Event	Arm A 3-DAA N = 325	Arm B Placebo N = 325	Arm A 3-DAA N = 205	Arm B Placebo N = 205	Arm A 3-DAA N = 60	Arm B Placebo N = 60	Arm A 3-DAA N = 60	Arm B Placebo N = 60
Any TEAE	191 (58.8)*	161 (49.5)	116 (56.6)	104 (50.7)	35 (58.3)	27 (45.0)	40 (66.7)	30 (50.0)
Serious TEAEs	7 (2.2)	2 (0.6)	4 (2.0)	2 (1.0)	1 (1.7)	0	2 (3.3)	0
TEAEs leading to DC of study drug	0[a]	3 (0.9)	0[a]	3 (1.5)	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0	0	0
All deaths[b]	0	0	0	0	0	0	0	0

DAA = direct-acting antiviral agent; DC = discontinuation; r = ritonavir; TEAE = treatment-emergent adverse event

a. An AE of cough was erroneously entered into the database as leading to discontinuation of study drug for 1 subject. This error was corrected after the database was locked for the PT Week 24 analyses. This subject completed study drug. Therefore, there is no AE leading to discontinuation of study drug in Arm A during the DB Treatment Period.

b. Includes non-treatment emergent deaths.

* Statistically significantly different from Arm B (placebo) at the $P = 0.05$ level.

Notes: *P* values for differences between treatment groups from Fisher's exact test. Only *P* values ≤ 0.05 are noted.
3-DAA = ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID.

During the DB Treatment Period, none of TEAEs occurred in more than 11.0% of subjects in either treatment group. The 2 most frequently reported TEAEs were upper respiratory tract infection and headache in the 3-DAA treatment group (Arm A) and upper respiratory tract infection and upper abdominal pain in the placebo group (Arm B). Overall, the AE profile was similar between the 2 treatment groups, with the exception of a higher frequency of pruritus, increased bilirubin, increased unconjugated bilirubin, and abdominal distension in the 3-DAA group and a higher frequency of upper abdominal pain with placebo.

No deaths have been reported.

A low frequency of serious AEs (2.2% and 0.6% of subjects in the 3-DAA and placebo groups, respectively) was reported during the DB Treatment Period. No commonality was identified among these events. Only 1 (0.3%) subject in the 3-DAA treatment group had a serious AE that the investigator considered to have a reasonable possibility of being related to DAA.

Summary/Conclusions (Continued)

Safety Results (Continued):

No subject on 3-DAA treatment discontinued study drug in the DB Treatment Period of the study due to a TEAE. One (Chinese) subject in Arm B receiving 3-DAA during the OL Treatment Period experienced TEAEs that led to premature discontinuation of study drug.

No subjects on the 3-DAA treatment during the DB or OL Treatment Period experienced any hepatic-related severe events. Low frequencies of subjects who received 3-DAA treatment in either the DB or OL Treatment Period experienced grade 3 or higher ALT elevation (DB: 2/325 [0.6%]; OL: 1/324 [0.3%]) or grade 3 or higher total bilirubin elevation (DB: 1/325 [0.3%]; OL: 1/324 [0.3%]). These ALT or bilirubin elevations were in general asymptomatic, transient without drug interruption or discontinuation, and none was associated with other liver function abnormalities. Bilirubin-related events of jaundice were reported with low frequency (DB: 1/325 [0.3%]; OL: 1/324 [0.3%]). There was no Hy's law case.

Four subjects had abnormal clinically significant ECG findings, all different, during treatment with 3-DAA accompanied by an associated AE. No other clinically meaningful results of vital signs or ECG evaluations were observed.

The 3-DAA regimen is a well-tolerated regimen for HCV patients without cirrhosis.

Conclusions:

- SVR_{12} and SVR_{24} were achieved by 99.5% of the treatment-naive subjects and all (100%) of the treatment-experienced subjects who received the 3-DAA regimen in the DB Treatment Period, with the LCB exceeding the superiority threshold for each rate. Therefore, the primary SVR_{12} and SVR_{24} endpoints were achieved, and 3-DAA demonstrated superiority to the historical control rate for therapy based on TVR plus pegIFN and RBV, irrespective of prior treatment status.
- The pharmacokinetics of the 3-DAA regimen are comparable among Chinese, Korean, and Taiwanese noncirrhotic HCV GT1b-infected subjects, and between those who received 3-DAA during the DB Treatment Period and those who received 3-DAA during the OL Treatment Period.
- The 3-DAA regimen was well-tolerated with no treatment discontinuations due to AEs, demonstrating a favorable safety profile, both overall and within each of the geographic regions of China, South Korea, and Taiwan. The safety profile of the 3-DAA in this study is consistent with that observed in previous studies.