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, ribavirin		
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 N-{6-[3-*tert*-butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl]naphthalen-2-yl}methanesulfonamide hydrate Ribavirin: 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide		

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 Co-administered with Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-I)

Investigator: Jordan Feld, MD

Study Sites:

79 investigative sites in the United States, Australia, Austria, Canada, France, Germany, Hungary, Italy, New Zealand, Spain, Sweden, Switzerland, and the United Kingdom

Publications: 2

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 27 November 2012 Last Subject Last Visit: 09 October 2014	

Objectives:

The primary objectives of this study were to show the noninferiority in SVR_{12} rates (the percentage of subjects achieving a 12-week sustained virologic response [HCV ribonucleic acid {RNA} < lower limit of quantitation {LLOQ} 12 weeks following therapy]) after 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV (the direct-acting antiviral agent [DAA] combination regimen) to the historical sustained virologic response (SVR) rate of telaprevir plus pegylated interferon (pegIFN) and RBV therapy and to assess the safety of the DAA combination regimen versus placebo for 12 weeks in HCV genotype 1-infected adults without cirrhosis.

The secondary objectives of this study were to measure the effect of the DAA combination regimen compared with placebo for 12 weeks on normalizing alanine aminotransferase (ALT) levels and demonstrate the effect of the DAA combination regimen on SVR_{12} in subjects with HCV genotype 1a and genotype 1b infection, and on HCV RNA levels during and after treatment as measured by on-treatment virologic failure and post-treatment (PT) relapse, respectively.

Methodology:

This was a Phase 3, randomized, double-blind (DB), placebo-controlled, multicenter study evaluating ABT-450/r/ABT-267 and ABT-333 co-administered with RBV in treatment-naïve, noncirrhotic HCV genotype 1-infected adults.

Approximately 600 HCV genotype 1-infected, treatment-naïve adults were randomized to Arms A and B in a 3:1 ratio in the DB Treatment Period at approximately 80 sites.

- Arm A: ABT-450/r/ABT-267 150 mg/100 mg/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) + RBV for 12 weeks (3-DAA + RBV);
- Arm B: Placebo for ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID + RBV for 12 weeks followed by ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID + RBV for 12 weeks.

RBV dosing was weight based, either 1,000 mg or 1,200 mg daily divided BID per local label (e.g., < 75 kg = 1,000 mg daily divided BID or ≥ 75 kg = 1,200 mg daily divided BID).

Methodology (Continued):

The duration of the study was up to 72 weeks (not including a screening period of up to 35 days), consisting of 3 periods: the DB Treatment Period, the Open-Label (OL) Treatment Period (for subjects randomized to placebo treatment group), and the PT Period (for all subjects who received active study drugs).

In the DB Treatment Period, randomization was stratified by HCV subtype (1a versus non-la) and interleukin 28B (IL28B) genotype (CC versus non-CC). Subjects randomized to placebo treatment were administered open-label active study drugs for 12 weeks following the DB Treatment Period.

All subjects administered active study drugs 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 [not required for the placebo treatment group during the OL and PT Periods]).

The primary analysis, as described in this report, occurred after subjects initially randomized to active drug completed through PT Week 12 or prematurely discontinued the study and subjects who were initially randomized to placebo completed 12 weeks of OL active treatment or prematurely discontinued study drug. A follow-up analysis will occur after subjects who received OL active treatment complete through PT Week 12 or prematurely discontinue the study at a date to correspond with the 120-day Safety Update. All remaining data through PT Week 48 will be summarized in the end-of-study analysis.

Safety evaluations occurred throughout the study by a Data Monitoring Committee. Efficacy evaluations occurred throughout the DB and OL Treatment Periods. If virologic failure criteria were met, the findings were discussed with the investigator.

Number of Subjects (Planned and Analyzed):

Approximately 600 subjects were planned; 631 subjects (473 in Arm A and 158 in Arm B) were enrolled and received at least 1 dose of study drug. One hundred fifty-seven (157) subjects in Arm B received open-label study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV genotype 1-infected treatment-naïve adults (18 to 70 years of age, inclusive), with a body mass index ≥ 18 to < 38 kg/m^2. Females were practicing abstinence, sexually active with female partners only, postmenopausal for at least 2 years, surgically sterile, or of childbearing potential and practicing 2 effective forms of birth control while receiving study drug. Males must have been surgically sterile or had male partners only or if with female partners must have agreed to practice 2 effective methods of birth control throughout the course of the study. Subjects were in a condition of general good health, other than the HCV infection. Subjects had a chronic HCV genotype 1 infection, a plasma HCV RNA > 10,000 IU/mL, a liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis (e.g., a Metavir score of 3 or less or an Ishak score of 4 or less) or FibroTest® score ≤ 0.72 and aspartate aminotransferase (AST) to platelet ratio index ≤ 2, or FibroScan® result < 9.6 kPa.

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/r/ ABT-267	Abbott/AbbVie	Oral	Tablet	75 mg/ 50 mg/ 12.5 mg	12-005439 12-005575
ABT-450/r/ ABT-267 placebo	Abbott/AbbVie	Oral	Tablet	0 mg	12-005189
ABT-333	Abbott/AbbVie	Oral	Tablet	250 mg	12-003124 12-003123
ABT-333 placebo	Abbott/AbbVie	Oral	Tablet	0 mg	12-002404
RBV tablets	Roche Pharma AG	Oral	Tablet	200 mg	12-005723
	Roche Pharma AG	Oral	Tablet	200 mg	12-005355
	Kadmon Pharmaceuticals, LLC[a]	Oral	Tablet	200 mg	12-004860
RBV capsules	Overencapsulated by: [redacted] for Abbott/AbbVie[b]	Oral	Hard Gelatin Capsule	200 mg	12-003231 12-003232 12-003233 12-004473
Placebo for overencapsulated RBV	Abbott/AbbVie	Oral	Hard Gelatin Capsule	0 mg	10-004370 12-002308

a. During the course of the study, DSM Pharmaceuticals Inc. manufactured for Three Rivers Pharmaceuticals, LLC and for Kadmon Pharmaceuticals, LLC. Kadmon Pharmaceuticals, LLC acquired Three River Pharmaceuticals.

b. Ribavirin tablets were commercial product RBV tablets used in overencapsulated lots 12-003231, 12-003232, and 12-003233 were manufactured at Roche Pharma AG. Ribavirin tablets used in overencapsulated lot 12-004473 were manufactured at Kadmon Pharmaceuticals, LLC.

Duration of Treatment:

In the DB Treatment Period, subjects received ABT-450/r/ABT-267 and ABT-333 co-administered with RBV or matching placebos for 12 weeks. Subjects randomized to placebo in the DB Treatment Period received ABT-450/r/ABT-267 and ABT-333 co-administered with RBV 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 post-treatment visits.

Criteria for Evaluation (Continued)

Resistance:

For subjects receiving active drugs who did not achieve SVR, the variants at signature resistance associated amino acid position by population nucleotide sequencing at baseline were compared with the appropriate prototypic reference sequence, and the variants at each amino acid position by population nucleotide sequencing at available postbaseline time points compared with baseline and the appropriate prototypic reference sequences were tabulated and summarized.

Patient-Reported Outcomes:

The change in disease-specific function and wellbeing were assessed using the HCV Patient-Reported Outcomes (HCV-PRO) instrument. Health State Utility was measured using the EuroQol-5 Dimensions-5 Levels Health State Instrument (EQ-5D-5L). General Health Related Quality of Life (HRQoL) was assessed using the Short Form 36 Version 2 health survey (SF-36v2) non-disease specific HRQoL instrument.

Pharmacokinetic:

Plasma concentrations for ABT-450, ritonavir, ABT-333, ABT-333 M1 metabolite, ABT-267, and RBV were determined in samples harvested at each study visit for Arm A subjects during the DB Treatment Period and Arm B subjects during the OL Treatment Period; the time of the last dose of study drug was also recorded.

Safety:

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

Statistical Methods

Efficacy:

The primary efficacy endpoints were:

- SVR_{12}: Noninferiority of the 3-DAA + RBV treatment group to the historical rate for telaprevir plus pegIFN and RBV; lower bound of 95% confidence interval (LCB) must have exceeded 70% to achieve noninferiority.
- SVR_{12}: Superiority of the 3-DAA + RBV treatment group to the historical rate for telaprevir plus pegIFN and RBV; LCB must have exceeded 80% to achieve superiority.

The following hypotheses were tested on subjects in the intent-to-treat (ITT) population who were randomized to active study drug (Arm A). To test the hypothesis that the percentage of treatment-naïve HCV genotype 1-infected subjects treated with ABT-450/r/ABT-267 + ABT-333 with RBV who achieved SVR_{12} is noninferior or superior to the historical SVR rate for the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage and 2-sided 95% confidence interval (CI) of subjects with SVR_{12} were calculated using the simple proportion and variance, and the normal approximation to the binomial distribution was used to estimate the CI. The LCB must have been > 70% in order for the regimen to be considered noninferior, and the LCB must have been > 80% in order for the regimen to be considered superior to the historical SVR rate in treatment-naïve HCV genotype 1-infected subjects without cirrhosis treated with telaprevir plus pegIFN and RBV.

Statistical Methods (Continued)

Efficacy (Continued):

The secondary efficacy endpoints included in the fixed-sequence testing procedure were:

1. ALT normalization rate during treatment in Arm A compared to Arm B.
2. Sustained virologic response 12 weeks postdosing (SVR_{12}): In HCV genotype 1a-infected subjects, for superiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV, the LCB must have exceeded 75%.
3. SVR_{12}: In HCV genotype 1b-infected subjects, for superiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV, the LCB must have exceeded 84%.

ALT normalization (final ALT ≤ upper limit of normal [ULN] in the Treatment Period for subjects with ALT > ULN at baseline) was calculated for all subjects in the ITT population with ALT above the ULN at baseline. To test the hypothesis that the percentage of subjects in the active arm with ALT normalization is greater than the percentage of subjects in the placebo arm with ALT normalization at the Final DB Visit, the treatment groups were compared using Fisher's exact test. If superiority of the active arm is demonstrated with a *P* value ≤ 0.05, then the DAA combination regimen was considered a success for this endpoint. To test the hypothesis that the percentage of treatment-naïve HCV genotype 1a subjects treated in Arm A who achieved SVR_{12} was superior to the historical SVR rate in the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with SVR_{12} was calculated with a 2-sided 95% CI calculated using the normal approximation to the binomial distribution. The LCB must have been greater than 75% in order for the regimen to be a success for this endpoint. To test the hypothesis that the percentage of treatment-naïve HCV genotype 1b subjects treated in Arm A who achieved SVR_{12} was superior to the historical SVR rate in the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with SVR_{12} was calculated with a 2-sided 95% CI calculated using the normal approximation to the binomial distribution. The LCB must have been greater than 84% in order for the regimen to be a success for this endpoint.

Other secondary endpoints not included in the fixed-sequence testing procedure were:

- The percentage of subjects in Arm A with on-treatment virologic failure during the DB Treatment Period (defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment or confirmed HCV RNA ≥ LLOQ at the end of treatment);
- The percentage of subjects in Arm A with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment).

The simple percentages and 2-sided 95% CIs using the normal approximation to the binomial distribution of the subjects with virologic failure during treatment and post-treatment relapse were calculated and summarized. These endpoints were not part of the fixed-sequence testing procedure as no hypothesis was being tested.

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 positions at baseline identified by population nucleotide sequencing were compared with the appropriate prototypic reference sequence, 2) the variants at available postbaseline time points identified by population nucleotide sequencing were compared with 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 for all subjects not achieving SVR, and 4) the persistence of viral resistance was summarized for all subjects not achieving SVR, regardless of the reason.

Patient-Reported Outcomes:

Exploratory analyses of the change in non-disease-specific HRQoL, HCV-specific function and wellbeing, and health state utility were measured using the SF-36v2, HCV-PRO, and EQ-5D-5L instruments, respectively. SF-36v2 and HCV-PRO were analyzed by their component total/component scores, as appropriate. The EQ-5D-5L was analyzed by utility score and by visual analogue scale (VAS) response. Change from baseline in the PRO summary measures was summarized and compared between treatment arms using analysis of covariance 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 group. The MIDs for the HCV-PRO total score and the EQ-5D-5L health index are based on receiver operating characteristic curve anchored by SF-36v2 Mental Component Summary and SF-36v2 Physical Component Summary decrease of 5 points.

Pharmacokinetic:

Individual plasma concentrations of ABT-450, ritonavir, ABT-333, ABT-333 M1 metabolite, ABT-267, and RBV were tabulated in relation to time of the last drug dose and summarized for subjects in Arm A from the DB Treatment Period and Arm B from the OL Treatment Period.

Safety:

The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and preferred term for each treatment arm; comparisons were performed between the active regimen and placebo during the DB Treatment Period using Fisher's exact test. Tabulations were also provided in which the number of subjects reporting an adverse event (MedDRA term) in each treatment group was additionally presented by rating (mild, moderate, or severe) and relationship to study drugs. Change from baseline in laboratory tests and vital sign measurements to each time point of collection during the DB Treatment Period was summarized by treatment group and compared between treatment groups using analysis of variance with treatment group as a factor. Laboratory and vital sign values that were potentially clinically significant (PCS), according to predefined criteria, were identified, and the percentage of subjects with PCS values during the DB Treatment Period were compared between treatment groups using Fisher's exact tests.

Summary/Conclusions

Efficacy Results:

The primary efficacy endpoints of noninferiority of the 3-DAA + RBV treatment group to the historical comparator in SVR_{12} was achieved by 456/473 (96.4%) subjects, with a 95% CI of 94.7% to 98.1%. The LCB was above 70% (noninferiority threshold) and above 80% (superiority threshold). Therefore, both primary endpoints were achieved. Only 1.7% of all 473 ITT subjects experienced true virologic failure (on-treatment rebound or post-treatment relapse by PT Week 12).

Sensitivity analyses that evaluated alternative methods to impute missing post-treatment virologic results were consistent with the primary analysis. A test of heterogeneity within the 3-DAA + RBV treatment group indicated no significant heterogeneity ($P = 0.233$) across the 4 randomization strata defined by IL28B (CC versus non-CC) and HCV genotype (1a versus non-1a). For all subgroups (except for 1 European country with < 15 subjects), the lower confidence bound for the SVR_{12} rate was above the prespecified noninferiority threshold of 70%.

All 3 ranked secondary endpoints were achieved:

- A statistically significantly ($P < 0.001$) greater proportion of subjects randomized to 3-DAA + RBV achieved normalization of ALT during treatment compared with subjects randomized to placebo (97.0% versus 15.8%);
- For the HCV genotype 1a subgroup, SVR_{12} was achieved in 95.7% (95% CI 93.4% – 97.9%). The LCB was above the prespecified threshold of 75%, demonstrating superiority to the historical telaprevir-based SVR rate;
- For the HCV genotype 1b subgroup, SVR_{12} was achieved in 98.0% (95% CI 95.8% – 100.0%). The LCB was above the prespecified threshold of 84%, demonstrating superiority to the historical telaprevir-based SVR rate.

For HCV genotype 1-infected adults without cirrhosis, noninferiority and superiority of 3-DAA + RBV SVR_{12} rate of 96.4% to the historical control rate for telaprevir-based therapy were demonstrated for SVR_{12} and only 8 of 473 ITT subjects (1.7%) experienced true virologic failure (on treatment virologic failure or post-treatment relapse by PT Week 12). Superiority to the historical control rate was demonstrated for both genotype 1a SVR_{12} rate (95.7%) and genotype 1b SVR_{12} rate (98.0%).

Resistance Results:

Resistance analyses of subjects in the PVF population comprised 12 subjects who were treated with active study drug during the DB Treatment Period (Arm A) and 7 subjects treated with active study drug in the OL Treatment Period (Arm B). One genotype 1a-infected subject (Subject [redacted] relapsed at PT Week 24, and was determined by phylogenetic analysis to be re-infected with an HCV genotype 1a isolate that was genetically distinct from the one present at baseline.

There was no statistically significant association between baseline variants at signature resistance-associated amino acid positions and treatment outcome. The predominant variants in the genotype 1a-infected subjects in the PVF population at the time of failure were D168V and R155K in NS3, M28T and Q30R in NS5A, and S556G in NS5B. The predominant variants in genotype 1b-infected subjects at the time of failure were D168V and Y56H in NS3, Y93H in NS5A, and S556G in NS5B. Ten of the 15 genotype 1a-infected and 3 of the 4 genotype 1b-infected subjects in the PVF population had resistance-associated variants in all 3 targets, (NS3, NS5A, and NS5B) at the time of failure.

Summary/Conclusions (Continued)

Resistance Results (Continued):

Among the 4 subjects in the non-PVF population with postbaseline sequencing available, 1 genotype 1a-infected subject had resistance-associated variants in all 3 targets. The other 3 subjects had no resistance-associated variants in NS3 or NS5B at the time of treatment discontinuation, but had variants in NS5A.

Treatment-emergent resistance-associated variants were observed in NS3, NS5A, and NS5B in 14, 12, and 9 of the 19 subjects in the PVF population, respectively. Variants in NS3 in genotype 1a-infected subjects declined through PT Week 24 (6/7, 86%) and further by PT Week 48 (0/5, 0%). Treatment-emergent resistance-associated variants in NS5A and NS5B in genotype 1a-infected subjects remained detectable at similar levels through PT Week 48. Trends in persistence of variants in genotype 1b could not be determined due to the low number of subjects with virologic failure who had sequence data at follow-up time points.

Patient-Reported Outcomes Results:

The majority of subjects who were treated with 3-DAA + RBV experienced decreases (that did not meet criteria to be considered of minimal importance) or increases from baseline 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:

Based on the binned trough plasma concentration values, the exposures of DAAs, ritonavir, and RBV from the OL Treatment Period of Arm B were generally comparable with the exposures from the DB Treatment Period of Arm A.

Safety Results:

The 3-DAA + RBV regimen was generally well tolerated with few subjects (0.6%) prematurely discontinuing study drug because of 1 or more treatment-emergent adverse events. A majority of subjects in the 3-DAA + RBV treatment group (87.9%) and the placebo treatment group (73.4%) experienced 1 or more treatment-emergent adverse event during the DB Treatment Period. Most of these subjects, however, experienced events that were mild in severity in both the 3-DAA + RBV and placebo treatment groups.

The most common treatment-emergent adverse events in the 3-DAA + RBV and placebo treatment groups were fatigue (34.5% and 28.5%, respectively) and headache (33.0% and 26.6%, respectively). The percentage of subjects with these events was not statistically significantly different between treatment groups. Of the treatment-emergent adverse events reported for $\geq 5.0\%$ of subjects in either treatment group, a statistically significantly ($P \leq 0.05$) greater percentage of subjects in the 3-DAA + RBV treatment group than in the placebo treatment group experienced nausea, pruritus, insomnia, diarrhea, asthenia, dyspnea, decreased appetite, dry skin, and anemia. Each of these events was generally assessed as mild in severity by the investigator.

The events of anemia and skin-related disorders, such as pruritus, rash, and dry skin, which were observed in this group, have been previously associated with RBV use in trials in HCV-infected individuals.

The treatment-emergent adverse event profile for subjects receiving 3-DAA + RBV during the OL Treatment Period was similar to that of the 3-DAA + RBV treatment group during the DB Treatment Period. The most common treatment-emergent adverse events were fatigue, headache, nausea, insomnia, diarrhea, and pruritus.

Summary/Conclusions (Continued)

Safety Results (Continued):

One death occurred after the DB Treatment Period. Subject [redacted] (3-DAA + RBV) died due to treatment-emergent adverse events of non-small cell lung cancer and mediastinal mass that began 15 days after the last dose of study drug. These events were considered by the investigator to have no reasonable possibility of relationship to DAA or RBV treatment; an alternative etiology of smoking/tobacco use was given.

One death occurred after the OL Treatment Period. Subject [redacted] died due to a nontreatment-emergent adverse event of hepatic failure that began 288 days after the last dose of study drug. The investigator considered this event to have no reasonable possibility of being related to study drugs with an alternative etiology of ongoing HCV infection in the setting of severe pyoderma gangrenosum treated with immunosuppressive agents including steroids complicated by active CMV and aspergillus infections. Subject [redacted] had experienced relapse of her HCV infection 2 weeks post-treatment (Day 183).

Ten (2.1%) subjects in the 3-DAA + RBV treatment group experienced treatment-emergent serious adverse events during the DB Treatment Period. No commonality was identified among these events. Only 2 (0.4%) subjects had events (acute respiratory failure and hypoxia in 1 subject and abdominal pain, chills, diarrhea, nausea, sinus tachycardia, ventricular extrasystoles, and vomiting in the second subject) assessed by the investigator as having a reasonable possibility of being related to DAAs. In a third subject (0.2%), the event of anemia was considered related only to RBV. While receiving 3-DAA + RBV during the OL Treatment Period, treatment-emergent serious adverse events were reported by 2 (1.3%) subjects. Both of these subjects had events considered to have no reasonable possibility of relationship to DAA treatment.

Treatment-emergent adverse events leading to discontinuation of study drug during the DB Treatment Period were reported by 0.6% of subjects in each treatment group. All 3 subjects who were discontinued from 3-DAA + RBV had serious adverse events, 2 of whom had events considered related to study drug. The overall low rate of study drug discontinuation for the 3-DAA + RBV treatment group affirms the general tolerability of the 3-DAA + RBV treatment regimen. A total of 3 (1.9%) subjects receiving 3-DAA + RBV during the OL Treatment Period experienced treatment-emergent adverse events that led to premature discontinuation of study drug; all of these events were considered by the investigator to have a reasonable possibility of relationship to DAA treatment. None of these events was serious.

Analyses of rash-related, hemoglobin values and anemia-related events, liver function test values and hepatic-related events and bilirubin-related events observed during this study showed no new or different pattern compared with other clinical trials of AbbVie DAAs with RBV.

During the DB Treatment Period, a greater percentage of subjects in the 3-DAA + RBV treatment group compared with the placebo treatment group experienced at least 1 adverse event that met the drug-induced rash company MedDRA query (CMQ) during the DB Treatment Period, the most common of which were pruritus and rash. No subject experienced a treatment-emergent adverse event that met the severe cutaneous reactions standardized MedDRA query. A similar percentage of subjects administered 3-DAA + RBV during the OL Treatment Period experienced a treatment-emergent adverse event that met the drug-induced rash CMQ.

Summary/Conclusions (Continued)

Safety Results (Continued):

Reductions in hemoglobin were observed in the 3-DAA + RBV treatment group, as evidenced by a mean decrease from baseline to the Final DB Treatment Period Visit and the percentage of subjects with postbaseline grade 2 hemoglobin values. Postbaseline grade 2 values occurred in 5.8% of subjects who received the 3-DAA + RBV regimen; no subject had a postbaseline hemoglobin value that was grade 3 or 4. No subject received a blood transfusion and only 1 subject received erythropoietin. Moreover, by PT Week 4, the mean hemoglobin for the 3-DAA + RBV treatment group had returned to near baseline levels. Similarly, 7.7% of subjects who received the 3-DAA + RBV regimen in the OL Treatment Period experienced grade 2 hemoglobin levels.

Fifty-five (11.7%) subjects in the 3-DAA + RBV treatment group experienced a total bilirubin elevation that was $\geq 2 \times$ ULN; few subjects experienced events of jaundice (0.8%) or ocular icterus (0.6%). There were no 3-DAA + RBV interruptions or discontinuations due to elevations in total bilirubin. A similar percentage of subjects administered 3-DAA+ RBV in the OL Treatment Period experienced total bilirubin elevations that were $\geq 2 \times$ ULN.

Four (0.9%) subjects who received the 3-DAA + RBV regimen had grade 3 ALT elevations during treatment in the DB Treatment Period. Two subjects were categorized as being in the Hy's Law quadrant of an evaluation of drug-induced serious hepatotoxicity (eDISH) plot but neither was assessed as meeting criteria for Hy's Law by the blinded external hepatic panel. One of these subjects discontinued an oral contraceptive (Marvelon) at the time of the ALT elevation after which ALT levels declined.
Two (1.3%) subjects who received the 3-DAA + RBV regimen in the OL Treatment Period had grade 3 ALT elevations. Two subjects were categorized as being in the Hy's Law quadrant of an eDISH plot but neither was assessed as meeting criteria for Hy's Law by the blinded external hepatic panel. One of these subjects, a postmenopausal woman, discontinued combination oral estrogen and testosterone therapy and interrupted study drug for 9 days. The subject completed study drug with a normal ALT level. All subjects with ALT elevations completed therapy and achieved SVR_{12}. The ALT elevations had declined from the peak at the end of therapy and were normal or grade 1 at the PT Week 4 Visit.

No clinically meaningful results of urinalysis, vital signs, or electrocardiograms were observed.

Conclusions:

A 12-week regimen of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV in HCV genotype 1-infected, treatment-naïve, noncirrhotic adults showed an SVR_{12} rate of 96.4%, which demonstrated both noninferiority and superiority to the historic rate for telaprevir plus pegIFN and RBV in HCV genotype 1-infected adults without cirrhosis. There were no changes to the overall conclusions from the interim CSR. Only 1.7% of all ITT subjects experienced virologic failure during or post-treatment. The treatment regimen was generally well tolerated with only 0.6% of subjects discontinuing study drug as a consequence of 1 or more adverse events. Adverse events reported were generally consistent with the established safety profile for RBV and those demonstrated for the combination of 3-DAAs with RBV in previous studies.

Date of Report: 09Jul2015