

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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ABT-450 was identified as a lead compound by AbbVie and Enanta Pharmaceuticals.

Investigators

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Definitions of Prior Response to Peginterferon/ribavirin Therapy

Relapsers received at least 36 weeks of peginterferon/ribavirin and had undetectable HCV RNA at the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up. Partial responders received at least 20 weeks of therapy and achieved $\geq 2 \log_{10}$ IU/mL reduction in HCV RNA at week 12(weeks 10–16), but failed to achieve HCV RNA undetectable at the end of treatment. Null-responders received at least 12 weeks of therapy and failed to achieve a 2 \log_{10} IU/mL reduction in HCV RNA at week 12(weeks 10–16); or received at least 4 weeks of therapy and achieved a $< 1 \log_{10}$ IU/mL reduction in HCV RNA at week 4.

Eligibility Criteria

Main Inclusion:

1. Male or female and age is between 18 and 70 years, inclusive, at time of screening.
2. Patient must have documentation that they were adherent to prior pegIFN/RBV combination therapy and meet one of the following categories:
 - Null responder:
 1. received at least 12 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a 2 \log_{10} IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16); or
 2. received at least 4 weeks of pegIFN/RBV for the treatment of HCV and achieved a $< 1 \log_{10}$ IU/mL reduction in HCV RNA at Week 4 (≥ 25 days); or
 - Partial responder: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved $\geq 2 \log_{10}$ IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment; or
 - Relapser: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at or after the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up

Viral loads documenting the type of prior non-response should be obtained during the previous pegIFN/RBV treatment. PegIFN/RBV therapy must have been completed no less than 2 months prior to the Screening Visit.

3. Chronic HCV infection is defined as one of the following:
 - Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or
 - Positive for anti-HCV Ab and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrollment with evidence of chronic hepatitis C disease).

4. Screening laboratory result indicating HCV genotype 1-infection.
5. Per local standard practice, documented results of one of the following:
 - 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, Ishak score of 4 or less; or
 - A screening FibroTest® score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2 ; or
 - A screening FibroScan® result of < 9.6 kPa.

Patients with a non-qualifying Fibrotest®/APRI or Fibroscan® result may only be enrolled if they have a qualifying liver biopsy performed within 24 months prior to or during screening.

6. Patient has plasma HCV RNA level $> 10,000$ IU/mL at Screening.

Main Exclusion:

1. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol.
2. Positive test result for Hepatitis B surface antigen (HBsAg) or anti-Human Immunodeficiency virus antibody (HIV Ab).
3. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level $> 8.5\%$, at the Screening Visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
4. Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis, e.g., a Metavir Score of >3 or Ishak score of > 4 .
5. Screening laboratory analyses showing any of the following abnormal laboratory results:
 - Alanine aminotransferase (ALT) $> 5 \times$ upper limit of normal (ULN)
 - Aspartate aminotransferase (AST) $> 5 \times$ ULN
 - Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min
 - Albumin $<$ Lower limit of normal (LLN)
 - Prothrombin time/International normalized ratio (INR) > 1.5 . Patients with a known inherited blood disorder may be enrolled with permission of the AbbVie Study Designated Physician even if the INR > 1.5
 - Hemoglobin $<$ LLN
 - Platelets $< 120,000$ cells per mm^3
 - Absolute neutrophil count (ANC) < 1500 cells/ μL (< 1200 cells/ μL for patients of African descent who are black)
 - Indirect bilirubin $> 1.5 \times$ ULN and direct bilirubin $>$ ULN

Randomization Methods

Patients were randomized to ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + weight-based RBV or placebo for 12 weeks in a 3:1 ratio at the start of the study on double-blind Day 1. The randomization schedule was stratified by type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) and HCV subgenotype (1a versus non-1a).

The number of relapsers to previous pegIFN/RBV treatment was limited to ≤ 120 patients. The total number of partial responders plus relapsers to previous pegIFN/RBV treatment was limited to ≤ 300 patients. The number of null responders with a $< 1 \log_{10}$ IU/mL HCV RNA reduction at Week 4 who received at least 4 weeks of pegIFN/RBV (null responder definition 2) was limited to about 25 patients.

At the screening visit, patients were assigned a unique patient number through the use of Interactive Response Technology (IRT). For patients who did not meet the study selection criteria, the site personnel contacted the IRT system and identified the patient as a screen failure.

Enrolled patients retained their patient number, assigned at the Screening Visit, throughout the study. For enrollment of eligible patients into the study, the site utilized the IRT system in order to receive unique study drug bottle/kit numbers and a unique randomization number. The randomization number was used only by the Sponsor for loading the treatment assignments into the database. The study drug kit numbers and randomization numbers were assigned according to schedules computer-generated before the start of the study by the AbbVie Statistics Department.

Contact information and user guidelines for IRT use were provided to each site. Upon receipt of study drugs, the site acknowledged receipt in the IRT system.

Collection of Samples for HCV RNA Measurement

Plasma samples for HCV RNA measurement were obtained at screening. Additional samples for HCV RNA measurement were obtained during the double-blind period on day 1 and during the double-blind and open-label periods at scheduled visits every 1-2 weeks through the final treatment visit or premature discontinuation. Following administration of the last dose of study drug, samples for HCV RNA measurement were collected at post-treatment weeks 2, 4, 8, 12, 24, 36, and 48 or at the time of premature discontinuation.

Virologic Failure Criteria

The following criteria were considered evidence of virologic failure leading to

discontinuation of study drug while the patient was being treated with active drugs:

- 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;
- Failure to achieve HCV RNA $<$ LLOQ by Week 6;
- Confirmed HCV RNA \geq LLOQ (defined as two consecutive HCV RNA measurements \geq LLOQ) at any point during treatment after HCV RNA $<$ LLOQ.

These criteria were evaluated by an unblinded independent third party during the double-blind treatment period for patients receiving active regimen during the double-blind period, and by the investigator during the open-label treatment period for patients who had received placebo during the double-blind period. If any of the above criteria were met, the patient discontinued study treatment.

Patients with HCV RNA $<$ LLOQ at the end of treatment who completed treatment (study drug duration ≥ 77 days), who had post-treatment HCV RNA available, and who had a confirmed HCV RNA \geq LLOQ (defined as 2 consecutive HCV RNA measurements \geq LLOQ) at any point in the post-treatment period were considered to have relapsed.

Resistance Testing

For resistance testing, HCV viral RNA was extracted from samples obtained at baseline and at the time of virologic failure. The target genes were amplified by RT-PCR and then nested PCR using primers appropriate for subtype 1a or 1b sequences encoding NS3/4A protease, NS5A, and/or NS5B polymerase. The nested PCR amplification product was used as the template for DNA sequencing of the population of amplified molecules, performed under GLP (Good Laboratory Practice) conditions in a CLIA (Clinical Laboratories Improvement Amendments)-certified reference laboratory. The DNA sequence from each baseline sample was translated into amino acid sequence and compared to the appropriate reference sequence (1a-H77 or 1b-Con1) in order to identify pre-existing resistance-associated variants. The DNA sequence from each post-baseline sample was translated into amino acid sequence and compared to the sequence from the corresponding baseline sample to identify resistance-associated amino acid variants that emerged as a result of treatment.

Noninferiority and Superiority Thresholds for SVR12 Primary and Secondary Endpoints

The telaprevir plus peginterferon/ribavirin historical control sustained virologic response rates for non-cirrhotic treatment-experienced patients were determined using data from the REALIZE study¹. The rates were based on a weighted average of relapsers, partial responders, and null-responders, with the weighting reflecting the distribution of patients expected to enroll in the current study.

The calculated historical control rate for the overall population was 65% (95% confidence interval[CI] 60-70). For the active regimen in this study to be considered superior to the historical SVR rate for telaprevir plus pegIFN and RBV, the lower bound of the 95% CI for the SVR12 rate for all patients receiving the active regimen needed to exceed 70%, the upper bound of the 95% CI for the historical control rate.

A non-inferiority margin of 10.5% was used. The non-inferiority margin of 10.5% is based on the telaprevir ILLUMINATE study which used the same non-inferiority margin. The active regimen in this study would be considered noninferior to the historical control if the lower bound of the 95% CI of the sustained virologic response 12 weeks post-treatment was greater than the upper confidence bound for historical control minus 10.5% (i.e., 60%).

Historical control rates of 59% (95% CI, 53-65) and 71% (95% CI, 64-77) were calculated for the HCV genotype 1a- and HCV genotype 1b-infected subpopulations, respectively, using data from the REALIZE study with adjustment factors to account for the exclusion of patients with cirrhosis from this study. If the lower confidence bound for the 95% CI of the sustained virologic response 12 weeks post-treatment exceeded 65% for HCV GT1a-infected patients or 77% for HCV GT1b-infected patients receiving the active regimen in this study, the active regimen would be considered superior to the historical control for the treatment of that subtype.

Estimated SVR Rates for Telaprevir-Based Therapy in Treatment-Experienced, Without Cirrhosis

	All T12/P48 ^b n/N (%)	REALIZE ^a	
		Projected Enrollment in Study M13-098 (%)	Population- Based Weighted Average % [95% CI]
Prior relapsers	198/229 (86)	30	65 [60, 70]
Prior partial responders	46/65 (71)	35	
Prior null responders	40/97 (41)	35	

a. US Prescribing Information for INCIVEK™ (telaprevir). Vertex Pharmaceuticals Incorporated; Cambridge, MA.

b. All GT1 treatment-experienced subjects without cirrhosis in the REALIZE study.

Estimated SVR Rates for Telaprevir-Based Therapy in Treatment-Experienced Subjects by Subgenotype

	REALIZE ^{†‡}				Projected Enrollment in M13-098 (%)	Population-Based Weighted Average % [95% CI]
	GT1a (Pooled T12/PR48) n/N (%)	With Increase for Excluding Cirrhotics (%)	GT1b (Pooled T12/PR48) n/N (%)	With Increase for Excluding Cirrhotics (%)		
Relapsers	119/142 (83.8)	84.3	123/140 (87.9)	88.4	30	GT1a
Partial responders	26/55 (47.3)	59.3	27/40 (67.5)	79.5	35	59 [53, 65]
Null responders	24/88 (27.3)	36.5	22/59 (37.3)	46.5	35	GT1b 71 [64, 77]

GT1a = genotype 1a; GT1b = genotype 1b

† US Prescribing Information for INCIVEK™ (telaprevir). Vertex Pharmaceuticals Incorporated; Cambridge, MA.

‡ Zeuzem S, Andreone P, Pol S, et al. REALIZE trial final results: telaprevir-based regimen for GT1 hepatitis c virus infection in patients with prior null response, partial response or relapse to peginterferon/ribavirin. J Hepatol. 2011;54Suppl:S3.

Sample Size

This study was planned to enroll 400 patients in a 3:1 ratio to ABT-450/r/ABT-267 + ABT-333 + RBV or placebo (300 patients randomized to active drug and 100 patients randomized to placebo). The primary efficacy endpoint of SVR12 was assessed within the patients randomized to active drug. With a sample size of 300 patients and assuming that 85% of the patients in randomized to active regimen would achieve SVR12, this study has greater than 90% power to demonstrate non-inferiority with a 2-sided 95% lower confidence bound greater than 60% and greater than 90% power to demonstrate superiority with a 2-sided 95% lower confidence bound greater than 70%. No adjustment for dropout was applicable because patients without data at Post-Treatment Week 12 (after imputing) were counted as failures for SVR12.

Ranked Efficacy Endpoint Analyses

The primary efficacy endpoint analyses tested (1) non-inferiority of the sustained virologic response (HCV RNA <lower limit of quantitation) 12 weeks post-treatment (SVR12) rate in patients receiving active regimen during the double-blind period to the historical rate for telaprevir plus pegylated interferon and ribavirin, and (2) superiority of SVR12 rate in patients receiving active regimen during the double-blind period to the historical rate for telaprevir plus pegIFN and RBV. The secondary efficacy endpoint analyses (3) compared alanine aminotransferase normalization rate during treatment in patients receiving active regimen and placebo during the double-blind period, (4) tested superiority of the SVR12 rate in HCV genotype 1a-infected patients in patients receiving active regimen during the double-blind period to the historical rate for telaprevir plus pegylated interferon and ribavirin in that population, and (5) tested superiority of the SVR12 rate in genotype 1b-infected patients in patients receiving active regimen during the double-blind period to the historical rate for telaprevir plus pegylated interferon and ribavirin in that population.

In order to control the Type I error rate at 0.05, a fixed-sequence testing procedure² was used to proceed through the primary and secondary efficacy endpoints in the order shown above.

Other secondary endpoint analyses not included in the fixed-sequence testing procedure were the percentage of patients receiving active regimen during the double-blind period with on-treatment virologic failure (including failure to suppress and rebound) and post-treatment relapse.

Subgroup Analyses

The percentage (and 2-sided confidence intervals) of patients with SVR12 for subgroups was calculated. Pre-specified subgroups included:

- Type of response to previous pegIFN/RBV treatment (null responder [also by definitions 1 and 2], partial responder, or relapser);
- HCV genotype 1 subtype (1a, 1b, other);
- Baseline HCV RNA level (< 800,000 IU/mL or ≥ 800,000 IU/mL);
- IL28B genotype (CC or non-CC);
- Sex (Male versus female);
- Age (< 55 versus ≥ 55 years);
- Race (Black versus non-black);
- Ethnicity (Hispanic versus no ethnicity);
- Geographic Region (North America, Europe, or Australia) and country (as appropriate);
- BMI (< 30 or ≥ 30 kg/m²);
- Baseline IP-10 (< 600 pg/mL or ≥ 600 pg/mL);
- Baseline fibrosis stage (F0–F1, F2, or ≥ F3).

The number and percentage of patients achieving SVR12 within each subgroup was provided for all subgroups. If there were 10 or more patients within the subgroup level (e.g., for sex, 10 or more females and 10 or more males), then 2-sided 95% confidence intervals were presented and calculated using the normal approximation to the binomial distribution.

Results: Superiority Analyses of SVR12 in HCV genotype 1a- and 1b-infected patients (Secondary Endpoints).

The SVR12 rates in patients receiving the active regimen during the double-blind period were 96.0%(95% CI, 93.0-98.9) and 96.7%(95% CI, 93.6-99.9), respectively, among HCV-infected patients with subtype 1a and 1b. These rates were superior to the historical control SVR rates for telaprevir and peginterferon/ribavirin for these subpopulations. See section on Noninferiority and Superiority Analyses for a description of the methods for this analysis.

Results: Serious Adverse Event Details

One patient receiving active regimen during the double blind period had a serious adverse event assessed by the investigator as having a reasonable possibility of being related direct-acting antivirals. This serious adverse event was acute transient stroke (also known as cerebrovascular accident or transient ischemic attack). This patient had risk factors for ischemic attack including hypertension, age, male sex, and atrial septal defect with shunt.

Results: Laboratory Abnormalities

Grade 3-4 ALT/AST elevations in patients receiving the active regimen were not concomitant with grade 3-4 bilirubin. There were no Hy's law cases.

Figure S1. SAPPHIRE-II Study Design.

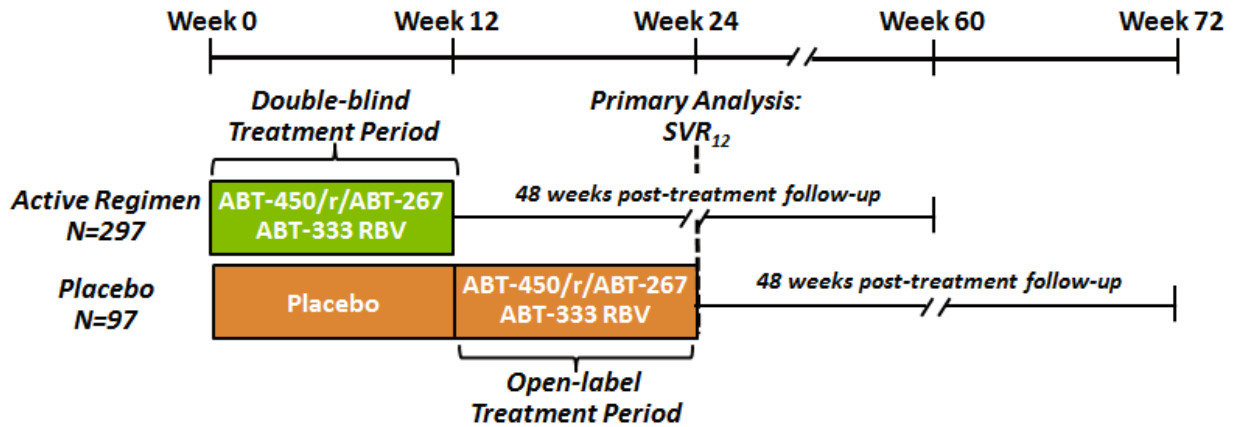


Figure S1. SAPPHIRE-II Study Design. During the 12-week double-blind period, patients received either ABT-450/r/ABT-267 and ABT-333 with ribavirin or placebo. Patients receiving placebo during the double-blind period, were treated with the active regimen for 12 weeks in open-label fashion at the conclusion of double-blind period. All patients administered the active regimen will be followed through 48 weeks post-treatment. RBV, ribavirin.

Figure S2. SAPPHERE-II Trial Profile.

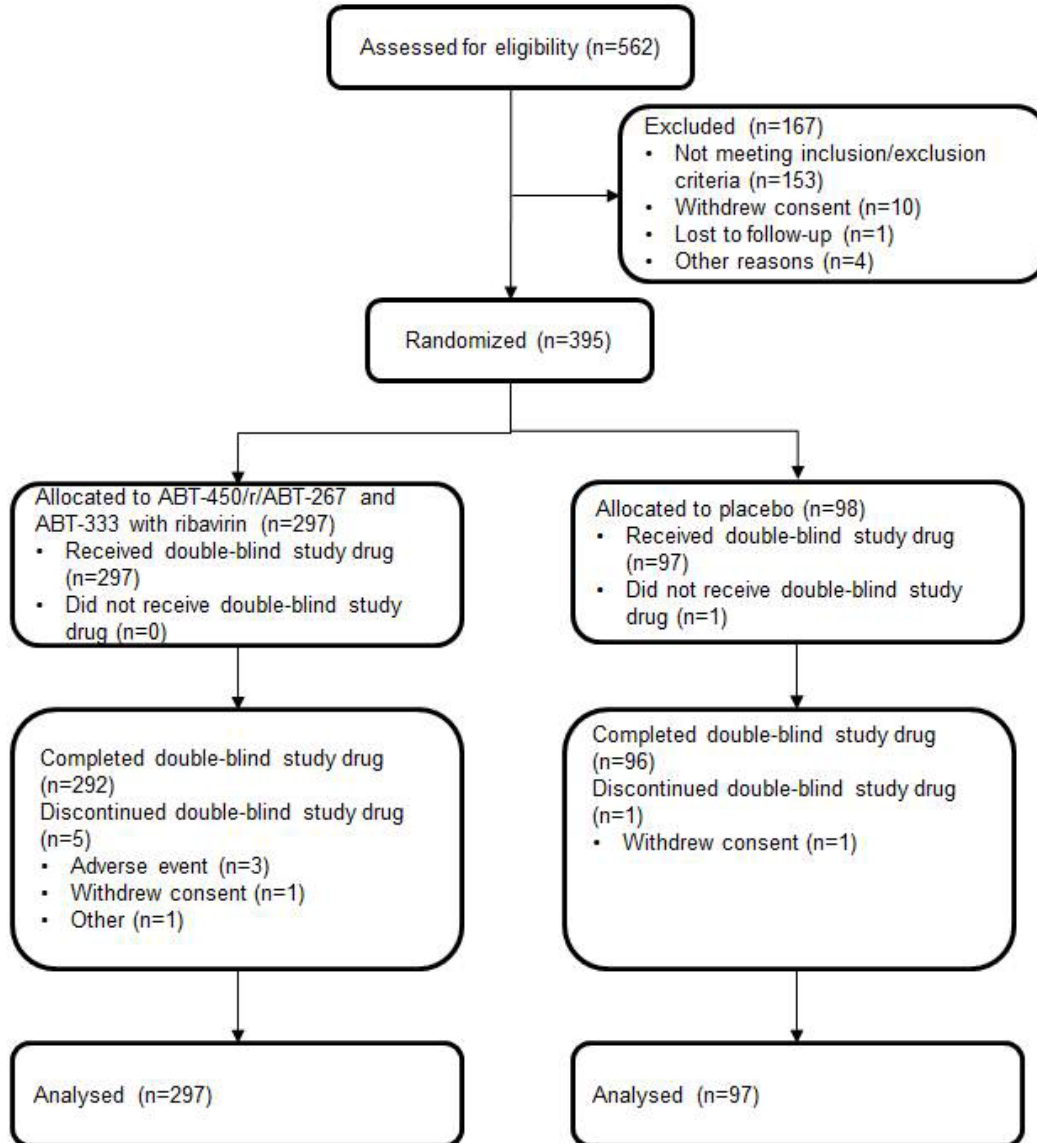


Figure S2. SAPPHERE-II trial profile. Peginterferon/ribavirin treatment-experienced patients with chronic HCV genotype 1 infection were assessed for eligibility and randomized to receive either ABT-450/r-ABT-267 and ABT-333 with ribavirin or placebo during the double-blind period. Further details on number of patients excluded due to specific inclusion/exclusion criteria are in Table S1.

Table S1. Reasons for screen failure due to not meeting inclusion/exclusion criteria.

Screened patients failing to meet inclusion criteria, n	Inclusion criteria
2	<p>Females must have negative results (unless otherwise noted below) for pregnancy tests performed:</p> <ul style="list-style-type: none"> ● at Screening by serum specimen within 35 days prior to initial study drug administration, and ● at Baseline (prior to dosing) by urine specimen. <p>Female patients with a borderline hCG result at Screening and /or Day 1 may enroll into the study if they either:</p> <ul style="list-style-type: none"> ● have a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy; or ● are confirmed to be postmenopausal defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state at Screening.
39	<p>Patient must have documentation that they were adherent to prior pegIFN/RBV combination therapy and meet one of the following categories:</p> <ul style="list-style-type: none"> ● Null responder: <ol style="list-style-type: none"> 1. received at least 12 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a 2 log₁₀ IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16); or 2. received at least 4 weeks of pegIFN/RBV for the treatment of HCV and achieved a < 1 log₁₀ IU/mL reduction in HCV RNA at Week 4 (≥ 25 days); or ● Partial responder: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved ≥ 2 log₁₀ IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment; or ● Relapser: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at or after the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up. <p>Viral loads documenting the type of prior non-response should be obtained in relation to the previous pegIFN/RBV treatment. PegIFN/RBV therapy must have been completed no less than 2 months prior to the Screening Visit.</p>
1	<p>Patients must be able to understand and adhere to the study visit schedule and all other protocol requirements.</p>

1	Body Mass Index (BMI) is from ≥ 18 to < 38 kg/m ² at the time of screening. BMI is calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m).
9	Screening laboratory result indicating HCV genotype 1-infection.
24	Per local standard practice, documented results of one of the following: <ul style="list-style-type: none"> ● 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, Ishak score of 4 or less; or ● A screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or ● A screening FibroScan result of < 9.6 kPa. Patients with a non-qualifying Fibrotest/APRI or Fibroscan result may only be enrolled if they have a qualifying liver biopsy performed within 24 months prior to or during screening.
Screened patients meeting exclusion criteria, n	Exclusion Criteria
2	Females who are pregnant or plan to become pregnant, or breastfeeding, or males whose partners are pregnant or planning to become pregnant within 7 months (or per local RBV label) after their last dose of study drug.
1	Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol.
1	Positive test result at screening for Hepatitis B surface antigen (HBsAg) or anti-Human immunodeficiency virus antibody (HIV Ab).
3	HCV genotype performed during screening indicates co infection with any genotype other than genotype 1.
5	Use of specified medications as well as those that are contraindicated for ritonavir and ribavirin within 2 weeks prior to study drug administration or 10 half-lives (if known), whichever is longer
13	Positive result of a urine drug screen at the Screening Visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, propoxyphene, or alcohol, with the exception of: <ul style="list-style-type: none"> ● a positive result associated with documented short-term use or chronic stable use of a prescribed medication in that class; ● a single positive result on urine screen for alcohol is discussed in Section 5.1.1.1 of the protocol on rescreening.

1	Clinically significant abnormalities, other than HCV infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile and a 12-lead electrocardiogram (ECG) that make the patient an unsuitable candidate for this study in the opinion of the investigator.
7	History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% at the Screening Visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
6	Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis, e.g., a Metavir score > 3 or an Ishak score > 4.
6	Any cause of liver disease other than chronic HCV infection, including but not limited to the following: <ul style="list-style-type: none"> ● Hemochromatosis ● Alpha-1 antitrypsin deficiency ● Wilson's disease ● Autoimmune hepatitis ● Alcoholic liver disease ● Drug-related liver disease Steatosis and steatohepatitis on a liver biopsy coincident with HCV-related changes would not be considered exclusionary unless the steatohepatitis is considered to be the primary cause of the liver disease.
40	Screening laboratory analyses showing any of the following abnormal laboratory results: <ul style="list-style-type: none"> ● ALT > 5 × Upper limit of normal (ULN) ● AST > 5 × ULN ● Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min ● Albumin < Lower limit of normal (LLN) ● Prothrombin time/International normalized ratio (INR) > 1.5. Patients with a known inherited blood disorder and INR > 1.5 may be enrolled with permission of the AbbVie Study Designated Physician ● Hemoglobin < LLN ● Platelets < 120,000 cells per mm³ ● Absolute neutrophil count (ANC) < 1500 cells/μL (< 1200 cells/μL for patients of African descent who are black) ● Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN
13	Clinically significant abnormal ECG, or ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 450 msec at Screening or

	DB Day 1 (prior to dosing).
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Note: Some patients failed screening due to multiple reasons

Table S2. Baseline fibrosis stage scoring.

Baseline Fibrosis Stage, Metavir Equivalents	Liver Biopsy Metavir, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec Score	Liver Biopsy Ishak Score	FibroScan® (kPa)	FibroTest®
F0-F1	0 or 1	0, 1, or 2	<8.8	≤0.48
F2	2	3	≥8.8 to <9.6	0.49 to 0.58
F3	3	4	≥9.6 to <14.6	≥0.59 to 0.72
F4	4	5 or 6	≥14.6	≥0.73

Baseline fibrosis stage is defined for patients with liver biopsy scores, FibroScan scores, or FibroTest scores available. Fibrosis score were determined by a single score in patients with multiple scores available. If a biopsy score was present, it was used to categorize the patient, regardless of the FibroScan/FibroTest score. Similarly, if a FibroScan score was present along with a FibroTest score, then the FibroScan score was used to categorize the patient.

Table S3. SVR12 rates by HCV subtype and prior peginteron/ribavirin response.

Previous Response to Peginterferon/Ribavirin	Overall n/N (%)	HCV Genotype 1a n/N (%)	HCV Genotype non-1a n/N (%)
Relapser	82/86 (95.3)	47/50 (94.0)	35/36 (97.2)
Partial responder	65/65 (100)	36/36 (100)	29/29 (100)
Null-responder	139/146 (95.2)	83/87 (95.4)	56/59 (94.9)

Subtype could not be determined in one patient. This patient, who was a prior partial responder, is included along with HCV genotype 1b-infected patients in the HCV genotype non-1a group.

Table S4. Treatment-emergent adverse events occurring in >5% of patients in either group during the double-blind period.

Event, n (%)	ABT-450/r/ABT-267 +ABT-333+Ribavirin N=297	Placebo N=97
Headache	108 (36.4)	34 (35.1)
Fatigue	99 (33.3)	22 (22.7)
Nausea	60 (20.2)	17 (17.5)
Asthenia	47 (15.8)	11 (11.3)
Insomnia	42 (14.1)	7 (7.2)
Pruritus	41 (13.8)*	5 (5.2)
Diarrhea	39 (13.1)	12 (12.4)
Dyspnea	37 (12.5)	10 (10.3)
Cough	32 (10.8)	5 (5.2)
Dizziness	26 (8.8)	5 (5.2)
Rash	26 (8.8)	6 (6.2)
Myalgia	23 (7.7)	10 (10.3)
Dry skin	22 (7.4)	3 (3.1)
Nasopharyngitis	21 (7.1)	5 (5.2)
Decreased appetite	20 (6.7)	2 (2.1)
Vomiting	20 (6.7) *	0
Arthralgia	19 (6.4)	7 (7.2)
Dyspepsia	17 (5.7)	3 (3.1)
Abdominal pain upper	16 (5.4)	6 (6.2)
Anemia	16 (5.4)*	0
Irritability	16 (5.4)	8 (8.2)
Back pain	15 (5.1)	3 (3.1)
Dyspnea exertional	12 (4.0)	5 (5.2)
Pruritus generalized	11 (3.7)	5 (5.2)
Dysgeusia	10 (3.4)	5 (5.2)
Depressed mood	5 (1.7)	5 (5.2)
Constipation	4 (1.3)	6 (6.2)*

*Significantly different from the rate in the other treatment group at the $P<0.05$ level. For comparison between treatment groups, $P=0.03$ for pruritus, $P=0.006$ for vomiting, $P=0.01$ for anemia, and $P=0.02$ for constipation. P values for comparisons between treatment groups were 0.06 for fatigue, 0.08 for insomnia, and 0.07 for depressed mood. P values for all other comparisons between treatment groups were >0.1 .

Table S5. Serious adverse events occurring during the double-blind period.

Serious Adverse Event	Group	Investigator Assessment of Relationship to ABT/450/r/ABT-267 + ABT-333 Treatment
Chronic obstructive pulmonary disease	Active regimen	No reasonable possibility
Acute transient stroke (cerebrovascular accident)*	Active regimen	Reasonable possibility
Pneumonia	Active regimen	No reasonable possibility
Acute renal failure [†]	Active regimen	No reasonable possibility
Intestinal obstruction	Active regimen	No reasonable possibility
Dizziness [‡]	Active regimen	No reasonable possibility
Nausea [‡]	Active regimen	No reasonable possibility
Vomiting [‡]	Active regimen	No reasonable possibility
Bradycardia [‡]	Active regimen	No reasonable possibility
Atrial fibrillation	Placebo	No reasonable possibility

*The patient experiencing acute transient stroke (also known as cerebrovascular accident or transient ischemic attack) had risk factors for ischemic attack including hypertension, age, male sex, and atrial septal defect with shunt.

[†]Acute renal failure onset was at day 1 of treatment. This patient discontinued study drug. Renal function normalized after study drug discontinuation. The investigator deemed the event as having no reasonable possibility of being related to direct-acting antivirals.

[‡]Occurred in 1 patient. Dizziness, nausea, and vomiting were intermittent and had a duration of 3 days beginning at day 70 of treatment. Bradycardia was intermittent and had a duration of 14 days beginning at day 71 of treatment. Study drug was interrupted. None of the events was assessed as having a reasonable possibility of being related to direct-acting antivirals.

Table S6. Hemoglobin Reductions During the Double-Blind Period.

	3D+RBV	Placebo
Baseline, n/N (%)*		
Grade 1 (<LLN-10.0 g/dL)	1/296 (0.3)	1/96 (1.0)
Grade 2 (<10.0-8.0 g/dL)	0/296	0/96
Grade 3 (<8.0-6.5 /dL)	0/296	0/96
Grade 4 (<6.5 g/dL)	0/296	0/96
Post-baseline, n/N (%)*		
Grade 1 (<LLN-10.0 g/dL)	154/296 (52.0)	2/96 (2.1)
Grade 2 (<10.0-8.0 g/dL)	14/296 (4.7)	0/96
Grade 3 (<8.0-6.5 /dL)	1/296 (0.3)	0/96
Grade 4 (<6.5 g/dL)	0/296	0/96

N=number of patients with a baseline and at least one post-baseline value through the final double-blind treatment value

References

1. Incivek (telaprevir) film coated tablets: US prescribing information. Cambridge, MA: Vertex Pharmaceuticals Inc, 2013. (Accessed at http://pi.vrtx.com/files/uspi_telaprevir.pdf Aug 20, 2013.).
2. Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. J Stat Plan Inference 2001;99:25-40.