Supplementary Appendix

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

Supplement to: Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. N Engl J Med. DOI: 10.1056/NEJMoa1315722

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

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Eligibility Criteria

Main Inclusion:

1. Male or female and age is between 18 and 70 years, inclusive, at time of Screening.
2. Female who is:
    - practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle)
    - sexually active with female partners only
    - postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state)
    - surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s)
    - of childbearing potential and sexually active with male partner(s):
        - currently using at least one effective method of birth control at the time of screening and agrees to using two effective methods of birth control while receiving study drugs (as outlined in the patient information and consent form or other patient information documents), starting with Study Day 1 and for 7 months after stopping study drug or as directedbythelocalribavirinlabel. (Note: Contraceptives containing ethinyl estradiol are not considered effective during study drug treatment.)
3. Sexually active males must be surgically sterile or have male partners only or if with female partner(s) of childbearing potential must agree to practice two effective forms of birth control (as outlined in the patient information and consent form or other patient information documents) throughout the course of the study, starting with Study Day 1 and for 7 months after stopping study drug or as directedbythelocalribavirinlabel.
4. Patient has never received antiviral treatment for hepatitis C infection.
5. 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.
6. Per local standard practice, documented results of one of the following:
    - 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
    - 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.)
7. 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 at screening 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 × upper limit of normal (ULN)
    - Aspartate aminotransferase (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 mm^3
    - 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

Randomization Methods

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.

Blinding

During the double-blind Treatment Period, measures to prevent implicit unblinding by laboratory results were used. Specifically, the results of HCV RNA, hemoglobin, hematocrit, ALT, AST, bilirubin (indirect and total), were blinded to the investigator, patient and Sponsor until the double-blind week 12 or premature discontinuation visit, unless criteria for virologic failure or

relevant predefined toxicity were met, in which case the relevant laboratory data were unblinded to the investigator, patient, and Sponsor.

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.

Plasma samples were also collected at screening to assess HCV genotype and subtype using the Versant HCV Genotype Inno-LiPA Assay, version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY), and for IL28B rs12979860 haplotype analysis.

Virologic Failure Criteria

The following criteria were considered evidence of virologic failure leading to discontinuation of study drug for individual patients 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 with at least 6 weeks treatment;
- Confirmed HCV RNA ≥ LLOQ (defined as two consecutive HCV RNA measurements ≥ LLOQ) at any point during treatment after HCV RNA < LLOQ.

There criteria were evaluated by an unblinded independent third party during the double-blind treatment period for patients in Arm A, and by the investigator during the open label treatment period for patients in Arm B. If any of the above criteria were met, the patient discontinued study treatment.

Patients who completed the treatment with HCV RNA < LLOQ at the end of treatment and who had a confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ 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 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. Each translated amino acid sequence from samples obtained at the time of virologic failure was compared to the sequence from the corresponding pretreatment sample in order to identify those amino acid variants that emerged or became enriched during direct-acting antiviral agent treatment.

Noninferiority and Superiority Analyses

Historical SVR rates, as reported in the telaprevir US Prescribing Information (USPI)[1] for telaprevir plus pegIFN and RBV treatment in various groups of treatment-naïve patients from the ADVANCE and ILLUMINATE trials are presented in the table below. For noncirrhotic genotype 1-infected patients, the upper bound of the 95% confidence interval (CI) is 80%, representing a threshold relevant to the overall population enrolled in this study.

SVR Rates for Telaprevir-Based Therapy in Treatment-Naïve Subjects

	ADVANCE	ILLUMINATE	Meta Analysis
Telaprevir Studies	**T12/PR n/N (%)**	**T12/PR n/N (%)**	**T12/PR % [95% CI]**
Treatment-naïve subjects without cirrhosis[1]	270/342 (79)	367/479 (77)	78 [75, 80]
Treatment-naïve GT1a subjects	162/217 (75)	273/388 (70)	72 [68, 75]
Treatment-naïve GT1b subjects	119/142 (84)	112/149 (75)	80 [75, 84]

GT1a = genotype 1a; GT1b = genotype 1b

For a regimen to be considered superior to the historical SVR rate for telaprevir, the lower bound of the 95% CI for the SVR rate for that regimen must exceed the upper confidence bound of the historical SVR rate for telaprevir based therapy presented in the table above (i.e., 80%). To be considered noninferior to the historical SVR rate for telaprevir, a margin of 10.5% is used. Thus, noninferiority to the historical SVR rate for telaprevir based therapy is obtained by showing the lower bound of the 95% CI for the SVR rate is greater than the upper confidence bound of SVR rate for the telaprevir based therapy minus 10.5% (i.e., 70%). The 2-sided 95% confidence intervals are created using the normal approximation to the binomial.

If the lower confidence bound for the 95% CI of the sustained virologic response 12 weeks post-treatment exceeded 75% for HCV GT1a-infected patients or 84% for HCV GT1b-infected patients receiving the active regimen in this study, the active regimen would be considered superior to the historical control for that treatment of that subtype.

Sample Size

This study was planned to enroll 600 patients in a 3:1 ratio to the DAA combination regimen or placebo (450 patients randomized to active drug and 150 patients randomized to placebo). The primary efficacy endpoint of SVR_{12} was assessed within the patients randomized to Arm A. With a sample size of 450 patients and assuming that 92% of the patients in Arm A will achieve SVR_{12}, this study has greater than 90% power to demonstrate non-inferiority with a 2-sided 95% lower confidence bound greater than 70% and greater than 90% power to demonstrate superiority with a 2-sided 95% lower confidence bound greater than 80%. No adjustment for dropout was applicable because patients without data at Post-Treatment Week 12 (after imputing) are counted as failures for SVR_{12}.

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 (SVR_{12}) rate in Arm A

to the historical rate for telaprevir plus pegylated interferon and ribavirin, and (2) superiority of SVR_{12} rate in Arm A to the historical rate for telaprevir plus pegIFN and RBV. The secondary efficacy endpoint analyses (3) compared alanine aminotransferase normalization rate during treatment in Arm A to Arm B, (4) tested superiority of the SVR_{12} rate in HCV genotype 1a-infected patients in Arm A to the historical rate for telaprevir plus pegylated interferon and ribavirin in that population, and (5) tested superiority of the SVR_{12} rate in genotype 1b-infected patients in Arm A 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 procedure[2] 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 are the percentage of patients in Arm A with on-treatment virologic failure (including failure to suppress and rebound) and post-treatment relapse.

Subgroup analyses

Pre-specified subgroup analyses were planned for all subgroups listed below including the pre-specified threshold shown. 95% confidence intervals used the normal approximation to the binomial distribution for subgroups with > 10 patients.

Subgroup (threshold):

- HCV genotype 1 subtype (1a, non-1a);
- IL28B genotype (CC or non-CC)
- Sex (male or female);
- Age (< 55 or ≥ 55 years)
- Birth year (< 1945, 1945 to 1965, > 1965);
- Race (Black or non-black);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Geographic Region (North America, Europe, or Australia/New Zealand) and Country (as appropriate);
- BMI (< 30 or ≥ 30 kg/m^2);
- Baseline HCV RNA levels (< 800,000 or ≥ 800,000 IU/mL);
- Baseline IP-10 (< 600 or ≥ 600 ng/L);
- Baseline HOMA-IR (< 3 or ≥ 3 mU × $mmol/L^2$);
- Baseline fibrosis stage (F0–F1, F2, or ≥ F3);
- History of Diabetes (yes/no);
- History of Depression or Bipolar Disorder (yes/no);
- History of Bleeding Disorders (yes/no);
- Former injection drug user (yes/no);
- RBV dose modifications (yes/no).

A stepwise logistic regression was performed to determine independent predictors of SVR_{12}. The pre-specified subgroup variables above were tested as predictors in this model, with the exception of HOMA-IR and IP-10 as many patients were missing these values. Baseline HCV RNA, age, and body-mass index were entered as continuous variables. Significance level for entering predictors into and removing predictors from the model was 0.10.

Figure S1. Trial Profile.

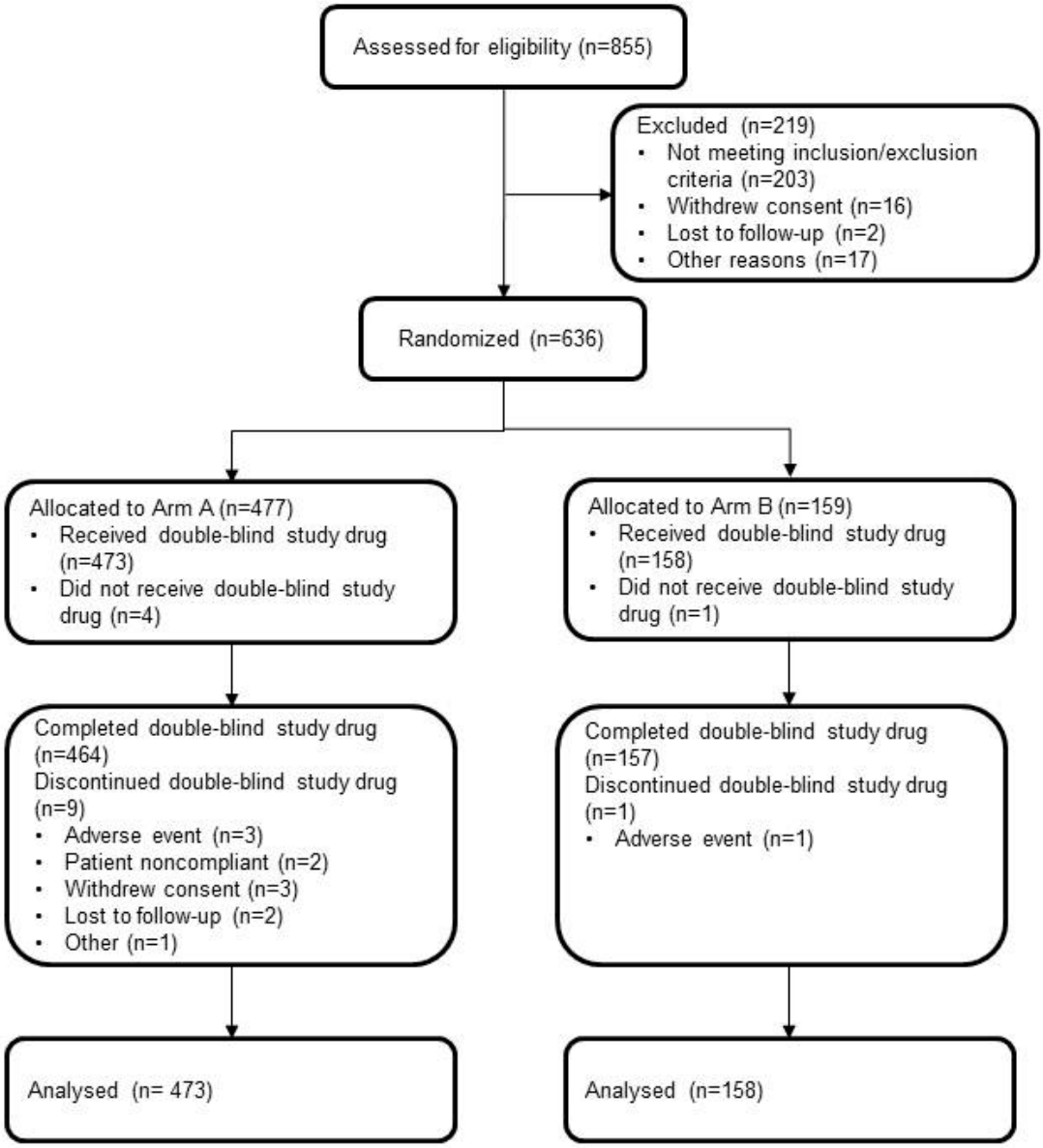

Figure S1. Trial profile. Treatment-naïve patients with chronic HCV genotype 1 infection were assessed for eligibility and randomized to receive either ABT-450/r/ABT-267 and ABT-333 with ribavirin or placebo during the double-blind period.

Figure S2. HCV RNA Suppression Over Time.

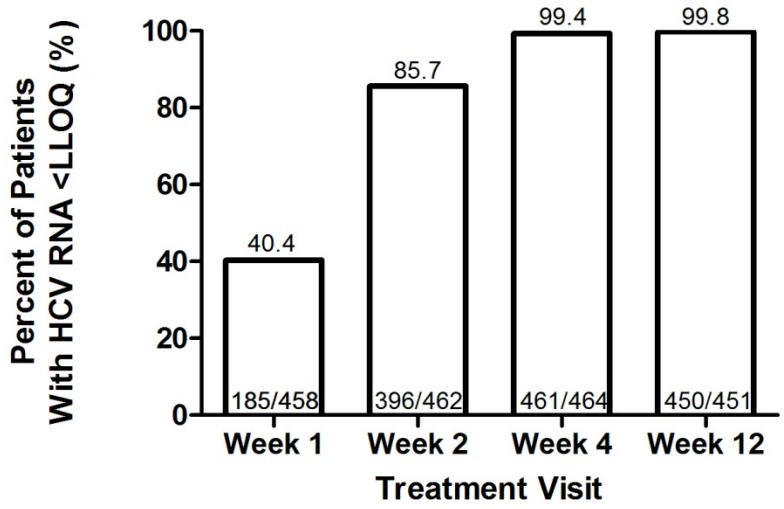

Figure S2. HCV RNA Suppression Over Time. Percent of patients in Arm A with HCV RNA <LLOQ at treatment visits, in patients with data at the treatment visit, during the double-blind period. Numbers in bars are n/N for each timepoint.

Table S1. Reasons for Screen Failure Due to Not Meeting Inclusion/Exclusion Criteria.

Screened patients failing to meet inclusion criteria, n	Inclusion criteria
1	Female who is: ● practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle) ● sexually active with female partners only ● postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state) ● surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s) ● of childbearing potential and sexually active with male partner(s): ○ of childbearing potential and sexually active with male partner(s) currently using at least one effective method of birth control at the time of screening and two effective methods of birth control while receiving study drugs (as outlined in the patient informed consent or other patient information documents), starting with Study Day 1 and for 7 months after stopping study drug as directed by the local ribavirin label. (Note: Hormonal contraceptives, including oral, topical, injectable or implantable varieties, may not be used during administration of study drugs.)
22	Females must have negative results for pregnancy tests performed: ● at Screening by serum specimen within 35 days prior to initial study drug administration, and ● at Baseline (prior to dosing) by urine specimen.
2	Patient has never received antiviral treatment for hepatitis C infection.
6	Patients must be able to understand and adhere to the study visit schedule and all other protocol requirements.
1	Must voluntarily sign and date an informed consent form, approved by an institutional review board (IRB)/independent ethics committee (IEC), prior to the initiation of any screening or study specific procedures.
5	Chronic HCV infection prior to study enrollment. 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.
24	Screening laboratory result indicating HCV genotype 1-infection.
45	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 or an 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 may only be enrolled if they have a qualifying liver biopsy performed within 24 months prior to or during screening.)
11	Patient has plasma HCV RNA level > 10,000 IU/mL at Screening.
Screened patients meeting exclusion criteria, n	**Exclusion Criteria**
1	Use of any herbal supplements (including milk thistle) within the 2-weeks or10 half-lives (if known) of the respective supplement, whichever is longer, prior to the first dose of study drugs.
1	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 drugs.
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 other genotype.
12	Use of specified concomitant 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
14	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: ● 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
3	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.
12	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.
1	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.

3	Any cause of liver disease other than chronic HCV infection, including but not limited to the following: ● Hemochromatosis ● Alpha-1 antitrypsin deficiency ● Wilson's disease ● Autoimmune hepatitis ● Alcoholic liver disease ● Nonalcoholic steatohepatitis ● Drug-related liver disease
79	Screening laboratory analyses showing any of the following abnormal laboratory results: ● 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 mm^3 ● 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
31	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).
4	Consideration by the investigator, for any reason, that the patient is an unsuitable candidate to receive ABT-267, ABT-333, ABT-450, ritonavir or RBV.
1	Current enrollment in another clinical study, previous enrollment in this study, or previous use of any investigational or commercially available anti-HCV agents including previous exposure to telaprevir, boceprevir, ABT-450, ABT-267, ABT-333 or RBV. Patients who previously participated in trials of investigational anti-HCV agents may be enrolled if they can produce documentation that they received only placebo. Concurrent participation in non-interventional, epidemiologic or registry trials may be permitted with approval from the AbbVie Study Designated Physician.
2	Uncontrolled clinically significant cardiac, respiratory (except mild asthma), hepatic (except HCV-related disease), gastrointestinal, hematologic or psychiatric disease or disorder, or any uncontrolled medical illness, which is unrelated to the hepatic disease.

Note: Some patients failed screening due to multiple reasons

Table S2. Fibrosis Scoring.

Baseline Fibrosis Stage, Metavir Equivalents	Liver Biopsy Metavir or Batts-Ludwig or Knodell or IASL or 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 will be 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. SVR_{12} Rates in Arm A According to Demographic and Baseline Clinical Characteristics.

Characteristic	Arm A	
	No./total no.	% (95% CI)
HCV subtype		
1a	307/322	95.3 (93.0, 97.6)
non-1a	148/151	98.0 (95.8, 100)
IL28B genotype		
CC	139/144	96.5 (93.5, 99.5)
Non-CC	316/329	96.0 (93.9, 98.2)
Gender		
Male	258/271	95.2 (92.7, 97.8)
Female	197/202	97.5 (95.4, 99.7)
Age		
<55 yr	280/290	96.6 (94.5, 98.7)
≥55 yr	175/183	95.6 (92.7, 98.6)
Birth year		
Before 1945	5/6	83.3 (NA)
1945 to 1965	289/301	96.0 (93.8, 98.2)
After 1965	161/166	97.0 (94.4, 99.6)
Race		
Black	27/28	96.4 (89.6, 100)
Non-black	428/445	96.2 (94.4, 98.0)
Ethnicity		
Hispanic/Latino	25/27	92.6 (82.7, 100)
Non-Hispanic/Latino	430/446	96.4 (94.7, 98.1)
Geographic region		
Australia/ New Zealand	32/33	97.0 (91.1, 100)
Europe	201/211	95.3 (92.4, 98.1)
North America	222/229	96.9 (94.7, 99.2)
Country		
AUS	26/26	100 (100, 100)
AUT	12/14	85.7 (67.4, 100)
CAN	33/34	97.1 (91.4, 100)
CHE	11/12	91.7 (76.0, 100)
DEU	35/36	97.2 (91.9, 100)
ESP	29/30	96.7 (90.2, 100)
FRA	30/33	90.9 (81.1, 100)
GBR	24/25	96.0 (88.3, 100)
HUN	19/19	100 (100, 100)
ITA	22/22	100 (100, 100)
NZL	6/7	85.7 (NA)

SWE	19/20	95.0 (85.5, 100)
USA	189/195	96.9 (94.5, 99.4)
BMI		
<30	390/402	97.0 (95.4, 98.7)
≥30	65/71	91.5 (85.1, 98.0)
HCV RNA		
<800,000 IU/mL	102/104	98.1 (95.4, 100)
≥800,000 IU/mL	353/369	95.7 (93.6, 97.7)
Baseline IP10		
<600 ng/L	362/375	96.5 (94.7, 98.4)
≥600 ng/L	62/66	93.9 (88.2, 99.7)
Missing	31/32	96.9 (90.9, 100)
Baseline HOMA-IR		
<3 mmol/L*μIU/mL	286/297	96.3 (94.2, 98.4)
≥3 mmol/L*μIU/mL	54/58	93.1 (86.6, 99.6)
Missing	115/118	97.5 (94.6, 100)
Fibrosis score		
F0-F1	352/363	97.0 (95.2, 98.7)
F2	66/70	94.3 (88.9, 99.7)
≥F3*	37/40	92.5 (84.3, 100)
History of Diabetes		
Yes	19/19	100 (100, 100)
No	436/454	96.0 (94.2, 97.8)
History of Depression or Bipolar Disorder		
Yes	66/70	94.3 (88.9, 99.7)
No	389/403	96.5 (94.7, 98.3)
History of Bleeding Disorders		
Yes	6/6	100 (NA)
No	449/467	96.1 (94.4, 97.9)
Former Injection Drug User Status		
Yes	196/205	95.6 (92.8, 98.4)
No	255/264	96.6 (94.4, 98.8)
Missing	4/4	100 (NA)
RBV Dose Modification		
Yes	29/31	93.5 (84.9, 100)
No	426/ 442	96.4 (94.6, 98.1)

*F3 only. No F4 patients were enrolled into the study.

Table S4. SVR12 Rates in Arm A By Body-Mass Index (Patients With BMI>30).

Body-Mass Index (kg/m^2)	No./total no.	%
30-<35	51/56	91.1
≥35	14/15	93.3

Analysis of SVR12 for patients with body-mass index 30-<35 kg/m^2 and >35 kg/m^2 was post-hoc.

Table S5. Treatment-Emergent Adverse Events Occurring in >5% of Patients in Either Arm During the Double-Blind Period.

Event, n (%)	Arm A N=473	Arm B N=158
Fatigue	34.7%	28.5%
Headache	33.0%	26.6%
Nausea	23.7%*	13.3%
Pruritus	16.9%*	3.8%
Insomnia	14.0%*	7.6%
Diarrhea	13.7%*	7.0%
Asthenia	12.1%*	3.8%
Rash	10.8%	5.7%
Dizziness	8.0%	3.8%
Dyspnea	8.0%*	2.5%
Decreased appetite	7.6%	3.2%
Cough	7.4%	5.1%
Nasopharyngitis	7.0%	6.3%
Abdominal pain upper	6.1%	3.2%
Dry skin	5.7%*	0.6%
Dyspepsia	5.5%	4.4%
Anemia	5.3%*	0
Irritability	5.3%	2.5%
Dyspnea exertional	5.1%	1.9%
Sleep disorder	5.1%	2.5%
Vomiting	5.1%	3.8%
Arthralgia	4.9%	5.7%
Upper respiratory tract infection	4.7%	5.1%
Myalgia	4.4%	5.1%
Dry mouth	3.8%	5.7%

Comparisons between groups were made using Fisher's exact test.

*Significantly different from the other arm at the 0.05 level.

Table S6. Treatment-Emergent Serious Adverse Events During the Double-Blind Period.

Serious Adverse Event	Investigator Assessment of Relationship to ABT/450/r/ABT-267+ABT-333 Treatment
Appendicitis	No reasonable possibility
Lobar pneumonia	No reasonable possibility
Cholecystitis	No reasonable possibility
Lumbar vertebral fracture (caused by car/bike accident)	No reasonable possibility
Aortic stenosis*	No reasonable possibility
Post-operative wound infection*	No reasonable possibility
Overdose†	No reasonable possibility
Encephalopathy†	No reasonable possibility
Mediastinal mass‡	No reasonable possibility
Non-small cell lung cancer‡	No reasonable possibility
Acute respiratory failure§	Reasonable possibility
Hypoxia§	Reasonable possibility
Abdominal pain‖	Reasonable possibility
Sinus tachycardia‖	Reasonable possibility
Diarrhea‖	Reasonable possibility
Chills‖	Reasonable possibility
Vomiting‖	Reasonable possibility
Nausea‖	Reasonable possibility
Ventricular extrasystoles‖	Reasonable possibility
Anemia**	No reasonable possibility
Non-cardiac chest pain**	No reasonable possibility

All events occurred in patients in Arm A.
*Occurred in 1 patient.
†Occurred in 1 patient.
‡Occurred in 1 patient.
§Occurred in 1 patient.
‖Occurred in 1 patient.
**Occurred in 1 patient.

Table S7. Hemoglobin Reductions During the Double-Blind Period.

n/N (%)	Arm A	Arm B
Baseline		
Grade 1, <LLN-10.0g/dL	2/469 (0.4)	0/158
Grade 2, <10.0-8.0g/dL	0/469	0/158
Grade 3, <8.0-6.5g/dL	0/469	0/158
Grade 4, <6.5g/dL	0/469	0/158
Post baseline		
Grade 1, <LLN-10.0g/dL	223/469(47.5)	4/158 (2.5)
Grade 2, <10.0-8.0g/dL	27/469 (5.8)	0
Grade 3, <8.0-6.5g/dL	0	0
Grade 4, <6.5g/dL	0	0

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.