Supplementary Appendix

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

Supplement to: Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med 2014;370:222-32. DOI: 10.1056/NEJMoa1306227

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

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Inclusion and Exclusion Criteria

Main inclusion:

1. Male or female between the age of 18 and 70 years, inclusive, at time of randomization.
2. If female, subject is either:
    - postmenopausal for at least 2 years (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone (FSH) level indicating a postmenopausal state), or
    - surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or
    - of childbearing potential subject and is currently practicing one of the following methods of birth control:
        - o total abstinence from sexual intercourse (minimum one complete menstrual cycle);
        - o vasectomized partner(s);
        - o intrauterine device (IUD); or
        - o double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or creams).
3. Female subjects of childbearing potential must be willing to use two effective forms of birth control (not including oral contraceptives or contraceptives containing ethinyl estradiol) throughout the study and for 6 months (or per local regulations) after stopping study drugs (refer to the list of effective birth control in the criteria above).
4. Females must have negative results for pregnancy tests performed:

• At Screening on a serum specimen obtained within 35 days prior to initial study drug administration, and

• On a urine sample obtained on Study Day 1 (prior to dosing).

5. Males must be surgically sterile or agree to practicing two effective forms of birth control as follows throughout the course of the study, starting with Study Day 1 and for 6 months after the last dose of study drugs:

• Abstinence,

• Partner(s) using an intrauterine device (IUD),

• Partner(s) using oral, injected, or implanted methods of hormonal contraceptives,

• Subject and/or partner(s) using double-barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams).

6. Subject must meet one of the following:

• Treatment-naïve: Subject has never received antiviral treatment for hepatitis C infection, OR

• Prior null responders: Subject has documentation that they previously received pegIFN plus ribavirin for at least 12 weeks and failed to achieve a 2 $\log_{10}$ HCV RNA decrease at Week 12. Subjects may be considered to meet this definition if the lack of treatment response was documented up to 2 weeks prior to treatment Week 12 with the approval of the Study Designated Physician.

7. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.

8. Body mass index (BMI) is > 18 to < 38 kg/m2. Body mass index is calculated as weight measured in kg divided by the square of height measured in meters (m).

9. Must voluntarily sign and date an informed consent, approved by an Institutional Review Board/Ethics Committee (IRB/EC), prior to the initiation of any screening or study-specific procedures.

10. Chronic HCV genotype 1-infection for at least 6 months prior to study enrollment. Chronic HCV infection is defined as one of the following:

- Positive for anti-HCV antibody or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV antibody at the time of Screening; or
- Positive for anti-HCV antibody 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).

11. Per local standard practice, documented results of:

- Fibro Test score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2 at Screening, or
- FibroScan® result of < 9.6 kPa, or
- the absence of cirrhosis based on a liver biopsy within the last 36 months.

12. Subject has a plasma HCV RNA level > 50,000 International Units (IU)/mL at Screening.

Main Exclusion:

1. History of severe, life-threatening or other significant sensitivity to any drug.

2. Use of any herbal supplements (including milk thistle) within the 2-week period prior to the first dose of study drug.

3. Females who are pregnant or breastfeeding or males whose partner is pregnant.

4. Recent (within 6-months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol.

5. Positive test result for hepatitis B surface antigen (HBsAg) or anti-HIV antibodies (anti-HIV Ab).

6. Use of any medications that are contraindicated for use with either ritonavir or ribavirin within 2 weeks prior to study drug administration or 10 half-lives whichever is longer.

- Amiodarone
- Bepridil
- Flecainide
- Propafenone
- Quinidine
- Ergot derivatives (e.g., dihydroergotamine, ergonovine)
- Oral midazolam or triazolam
- Pimozide
- Lovastatin, simvastatin
- Cisapride
- Alfuzosin HCl Refer to the most current package inserts for a complete list of contraindicated medications.

7. Use of known inhibitors (e.g., ketoconazole) or inducers (e.g., phenobarbital, rifampin, carbamazepine, St. John's Wort) of cytochrome P450 3A (CYP3A), cytochrome P450 2C8 (CYP2C8) (e.g., gemfibrozil, montelukast) and organic anion transporting polypeptide 1B1 (OATP1B1), (e.g., cyclosporine) within 1 month prior to study drug administration.

8. Positive result of a urine drug screen at the Screening Visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, and propoxyphene with the exception of a positive result (including methadone),

associated with documented short-term use or chronic stable use of a prescribed medication in that class.

9. 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 subject an unsuitable candidate for this study in the opinion of the Investigator.

10. History of uncontrolled seizures, cancer (except basal cell carcinoma of the skin), or uncontrolled diabetes, as defined by a hemoglobin A1C level > 8.0%.

11. Any current or past clinical evidence of cirrhosis (e.g., ascites, esophageal varices), or a liver biopsy showing cirrhosis.

12. 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

13. Screening laboratory analyses show any of the following abnormal laboratory results:

- Alanine aminotransferase (ALT) > 5 X upper limit of normal (ULN),
- Aspartate aminotransferase (AST) > 5 X ULN,
- Calculated creatinine clearance (using Cockcroft-Gault method) < 50 mL/min,
- Albumin < lower limit of normal (LLN),
- Prothrombin time INR > 1.5,

- Hemoglobin < LLN,
- Platelets < 120,000 cells per mm^3 for subjects with METAVIR score < 3 or Ishak score < 4 on a biopsy within the last 3 years; f for subjects with METAVIR score of 3 or Ishak score of 4, platelets < LLN,
- Absolute neutrophil count < 1500 cells/µL,
- Total bilirubin > 1.5 mg/dL,
- HCV RNA levels that are above the level of assay quantification.

14. Clinically significant abnormal ECG or ECG with QTc using Fridericia's correction formula (QTcF) > 450 msec at Screening or Day 1 (prior to dosing).

15. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks prior to study drug administration.

16. Consideration by the Investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-450, ABT-267, ABT-333, ritonavir, or ribavirin.

17. Current enrollment in another clinical study or previous use of any investigational or commercially available anti-HCV agents including previous exposure to ABT-450, ABT-267, ABT-333, ritonavir.

18. The use of colony stimulating factors, such as granulocyte colony stimulating factor (GCSF) or erythropoietin within 2 months of the Screening Period.

If there were multiple assessments on the same date for a subject, fibrosis score was calculated in the order of liver biopsy, FibroScan, and Fibro Test. If there were assessments on different dates for a subject by different methods, fibrosis score was calculated in the order of liver biopsy, FibroScan, and Fibro Test. If there were assessments on different dates for a subject by the same method, fibrosis score was calculated by maximum value.

Randomization

Randomization was via the Interactive Response Technology (IRT) system. For randomization of eligible patients, the site contacted the IRT to receive a unique randomization number and study drug kit numbers. The study drug kit numbers were assigned according to a randomization schedule computer-generated before the start of the study by the sponsor's statistics department.

Subjects were stratified by IL28B genotype (CC versus non-CC) and HCV genotype and subtype (1a versus non-1a). Subjects were enrolled in Cohort 1 (Treatment-naïve patients) or Cohort 2 (Prior null responders) according to their previous treatment status. For treatment-naïve subjects, enrollment into Groups A, F and G was preferential in that subjects were initially randomized in a 2:0:0:0:0:1:1:0:0 ratio to Groups A – I. When a total of 80 subjects were enrolled in this manner (40 subjects are enrolled in Group A and 20 subjects are enrolled in each of Groups F and G), the randomization continued in a 2:2:2:2:4:1:1:2:2 ratio to Group A – I up to a total of approximately 440 treatment-naïve subjects. Null responder subjects were randomized in a 2:1:1:1:1 ratio to Groups J – N up to approximately 120 subjects.

Collection of Samples for HCV RNA Measurement and Resistance Testing

Plasma samples for HCV RNA measurement and resistance testing were obtained on days 1 and 3, and at scheduled visits every 1-4 weeks through the final treatment visit or premature discontinuation. Following administration of the last dose of study drug, samples for HCV RNA measurement and resistance testing were collected at post-treatment weeks 2, 4, 8, 12, 24, and 48.

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.

HCV RNA Measurement

For HCV RNA measurement, samples were processed by a certified central laboratory using COBAS TaqMan® real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay, with a lower limit of detection of 15 IU/mL and a lower limit of quantitation of 25 IU/mL.

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. In addition, clonal sequencing was performed on the samples obtained at baseline and at the time of virologic failure.

The NS5A PCR product, NS5B PCR product, or a secondary PCR product containing the protease catalytic domain generated from the larger NS3/4A RT-PCR product was inserted into a DNA plasmid vector, transformed into an *E. coli* host, and plasmid DNA from individual colonies was purified. The inserted NS3 protease, NS5A, or NS5B polymerase gene was sequenced from 60-92 clones per sample. 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.

Virologic Failure Criteria

The following criteria were considered evidence of virologic failure:

- Failure to achieve an HCV RNA decrease of at least 2 $\log_{10}$ IU/mL at week 1.
- Confirmed increase from nadir (defined as 2 consecutive HCV RNA measurements >1 $\log_{10}$ above nadir) in HCV RNA level at any time point.
- Failure to achieve HCV RNA <25 IU/mL (detected or not detected) at week 6.
- Confirmed HCV RNA >25 IU/mL (defined as two consecutive HCV RNA measurements >25 IU/mL) at any point after HCV RNA <25 IU/mL.

All patients meeting criteria for on-treatment virologic failure were required to discontinue study drug treatment as soon as virologic failure was confirmed and were offered peginterferon plus ribavirn for up to 48 weeks, unless the investigator and sponsor agreed that continued study drug treatment was in the patient's best interest.

Primary and Secondary Efficacy Analyses

Primary Efficacy Analysis

The primary efficacy endpoint was the comparison of the percentage of treatment-naïve subjects with SVR_{24} following 8 weeks of treatment with 3 direct-acting antiviral agents (with ABT-450/r 150/100 mg) and ribavirin versus 12 weeks of treatment with 3 direct-acting antiviral agents (with ABT-450/r 150/100 mg) and ribavirin (Group A versus Group G). Logistic regression with treatment group, baseline $\log_{10}$ HCV RNA level, HCV subgenotype (1a or non-1a), geographic regions and IL28B genotype (CC, non-CC) as predictors was used to compare the groups.

Secondary Efficacy Analyses

The secondary efficacy endpoints were comparisons of the percentage of subjects with SVR_{24}:

1. among the subjects treated with 3 direct-acting antiviral agents + ribavirin for 8 weeks versus 12 weeks (Group A versus Groups[F + G + K + L], among subjects treated with 3 direct-acting antiviral agents + ribavirin for 8 versus 24 weeks (Group A versus Groups [H + I + M + N] and among subjects treated with 3 direct-acting antiviral agents + ribavirin for 12 weeks versus 24 weeks (Groups [F + G + K + L] versus Groups [H + I + M + N]),
2. among the subjects treated with 2 direct-acting antiviral agents (ABT-450/r + ABT-333) + ribavirin for 12 weeks versus 3 direct-acting antiviral agents + ribavirin for 12 weeks (Group B versus Groups [F + G + K + L]),
3. among the subjects treated with 2 direct-acting antiviral agents (ABT-450/r + ABT-267) + ribavirin for 12 weeks versus 3 direct-acting antiviral agents + ribavirin for

12 weeks (Groups [C + D + J] versus Groups [F + G + K + L]), among those treated with 3 direct-acting antiviral agents + ribavirin for 12 weeks versus 3 direct-acting antiviral agents without ribavirin for 12 weeks (Groups [F + G+ K + L] versus Group E), and

4. among treatment-naïve subjects and null responder subjects treated with ABT 450/r + ABT-267 + ABT-333 + ribavirin for 12 or 24 weeks (a combination of Groups F, G, H and I versus a combination of Groups K, L, M, and N).

The percentage of subjects with SVR_{24} were compared between the above specified treatment groups using logistic regression with treatment group, baseline $\log_{10}$ HCV RNA level, HCV subgenotype (1a or non-1a), geographic region, IL28B genotype (CC, non-CC), and ABT-450/r dose and subject populations (treatment-naïve versus null responder, if appropriate) as predictors. The stratum-adjusted Mantel-Haenszel (MH) method, controlling for the baseline stratification variables (IL28B genotype [CC and non-CC] and HCV subgenotype [1a and non-1a]), was also planned for the comparisons of SVR endpoints among the specific groups. It is also presented as the logistic regression analysis encountered separation or quasi-separation among the predictor variables due to the low number of subject failing to achieve SVR.

Sample Size Determination

For the primary efficacy endpoint of $SVR_{24actual}$, if we assume a rate of $SVR_{24actual}$ of 66% in Group A and 90% in Group G, 80 subjects in Group A and 40 subjects in Group G would provide 80% power using Fisher's exact test with a two-sided significance level of 0.05 to detect a difference of approximately 24% between the 2 groups. On the other hand, when comparing the comparable groups in Cohort 1 (Groups F, G, H, and I) and Cohort 2 (Groups K, L, M, and N), 160 subjects in the first set of groups and 80 subjects

in the second set of groups provide > 80% power to detect a difference of approximately 17% in $SVR_{24actual}$ rates (87% versus 70%) between the 2 sets of groups.

Interim Analyses and Stopping Guidelines

There will be interim analyses of all data after all subjects have completed treatment or prematurely discontinued study drug, after all subjects have reached Post-Treatment Week 12 or prematurely discontinued study, and after all subjects have reached Post-Treatment Week 24 or prematurely discontinued study. For each of these overall interim analyses, appropriate data base clean up procedures will be performed. There will be no statistical adjustment employed due to these analyses as this is an open-label trial.

Additional interim evaluations were performed to allow any inefficacious treatment group to be terminated from further enrollment. Interim HCV RNA data was used to calculate the posterior probability that each treatment group would achieve sustained virologic response 12 weeks post-treatment (SVR_{12}) rates >75% and that each treatment group would not be 10% worse than the 12 week groups with 3 direct-acting antiviral agents and ribavirin (Groups F+G) for treatment-naïve subjects or the 24 week groups with 3 direct-acting antiviral agents and ribavirin (Groups M+N) for null responder subjects. If at any of the interim evaluation, the posterior probability that one or more treatment groups will achieve SVR_{12} rates >75% is less than 10%, that group(s) may be discontinued from further enrollment for lack of efficacy. In addition, if the posterior probability that Group A, B, C, D, or E has SVR_{12} rates within 10% of Groups (F+G) is less than15%, or that Group J, K, or L has SVR_{12} rates within 10% of Groups (M+N) is less than15%, that treatment group may be discontinued from further enrollment.). The 24-week treatment groups, Groups H, I, M, and N, will not be discontinued for lack of efficacy because they

represent the maximum treatment regimen (3 direct-acting antiviral agents and ribavirin) for the maximum duration in each Cohort, and Groups F and G will not be discontinued because they are considered the comparator arm. An internal statistician will review the interim efficacy data and make recommendation to AbbVie on the fate of the treatment groups. The decision to stop enrollment to a particular group will be blinded to site staff and Investigators who are involved in the study. In the event that one of more treatment groups is discontinued, no additional subjects will be enrolled in that group(s) while subjects currently enrolled in the group will complete all planned dosing and follow-up. Additionally, enrollment in any study group(s) may be delayed prior to initiation, or paused during the study, based on available efficacy or safety data from this study or other ongoing studies.

Enrollment in any study group could also be discontinued at any time if ongoing data review revealed a potential risk to subject safety.

Results: Laboratory values

Details of bilirubin elevations

Eleven patients (2%; 7 treatment-naïve patients, 4 prior null responders) experienced grade 3 bilirubin elevations, 10 patients on a single measurement only. Among patients with grade 3 bilirubin elevation, 3 experienced jaundice, 1 additional patient had cholelithiasis, and 1 additional patient experienced acute cholestatic hepatitis with cholelithiasis on ultrasound. The acute cholestatic hepatitis event was considered possibly related to study drug and led to treatment discontinuation. The patient with acute cholestatic hepatitis had a maximum ALT value of 162 U/L, maximum AST value of 74 U/L, maximum alkaline phosphatase value was 99 U/L, maximum total bilirubin value of 4.3 mg/dL (74 μmol/L), maximum direct bilirubin value of 2.0 mg/dL (34 μmol/L),

and prothrombin time of 11.0 seconds. No other patients with grade 3 bilirubin elevation required study-drug interruption. No subject with elevated ALT had concomitant elevation in the prothrombin time.

Details of ALT elevations

Five patients (1%; 4 treatment-naïve patients, 1 prior null responder) experienced Grade 3 ALT elevations (maximum ALT level, 408 U/L). All were asymptomatic, with no concomitantly increasing bilirubin. ALT levels normalized in each case without study-drug interruption. Four of these 5 patients were receiving the highest ABT-450/r dose (200/100 mg daily).

Figure S1.Screening, enrollment, randomization, and follow-up of study patients.

Figure S1A.

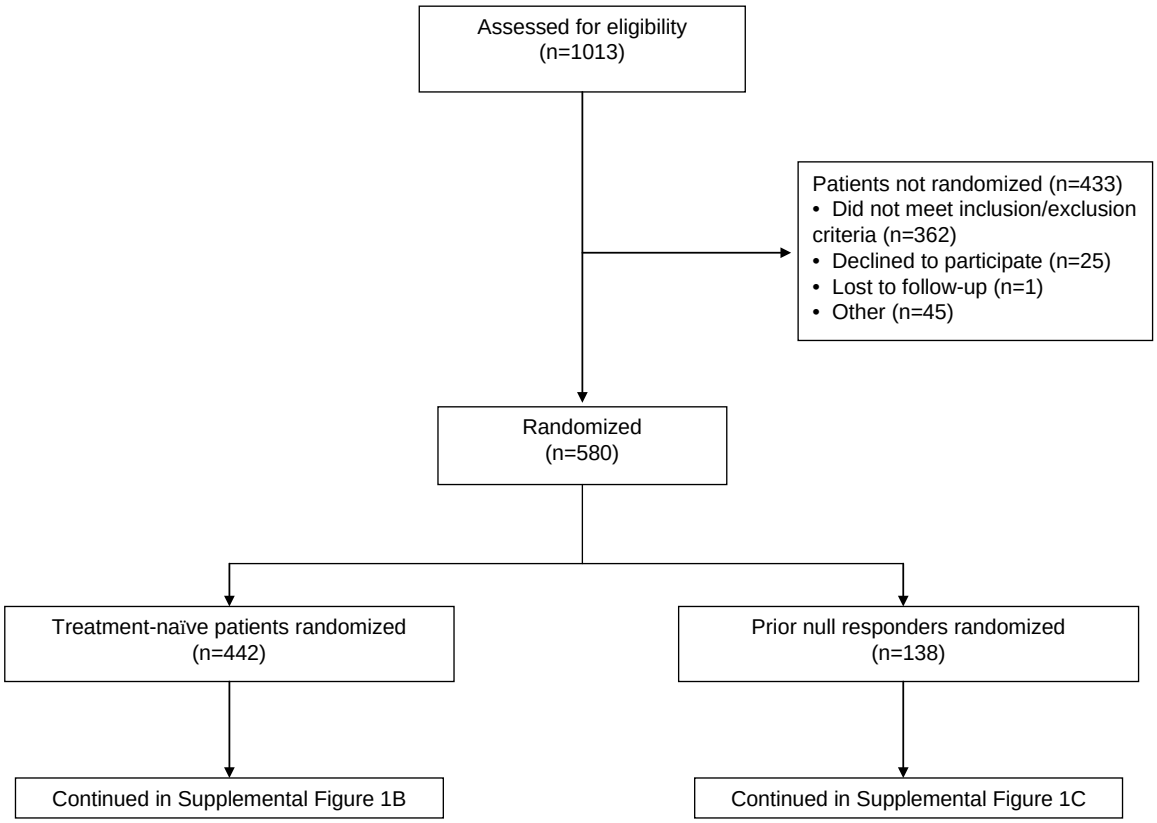

Figure S1. Patients were assessed for eligibility (S1A); treatment-naïve patients (S1B) and prior null responders (S1C) with chronic hepatitis C were randomized to receive a combination regimen of ABT-450/r with ABT-267, and/or ABT-333, and/or weight-based ribavirin. Duration of treatment was 8, 12, or 24 weeks. Follow-up was through 48 weeks post-treatment.

Figure S1B.

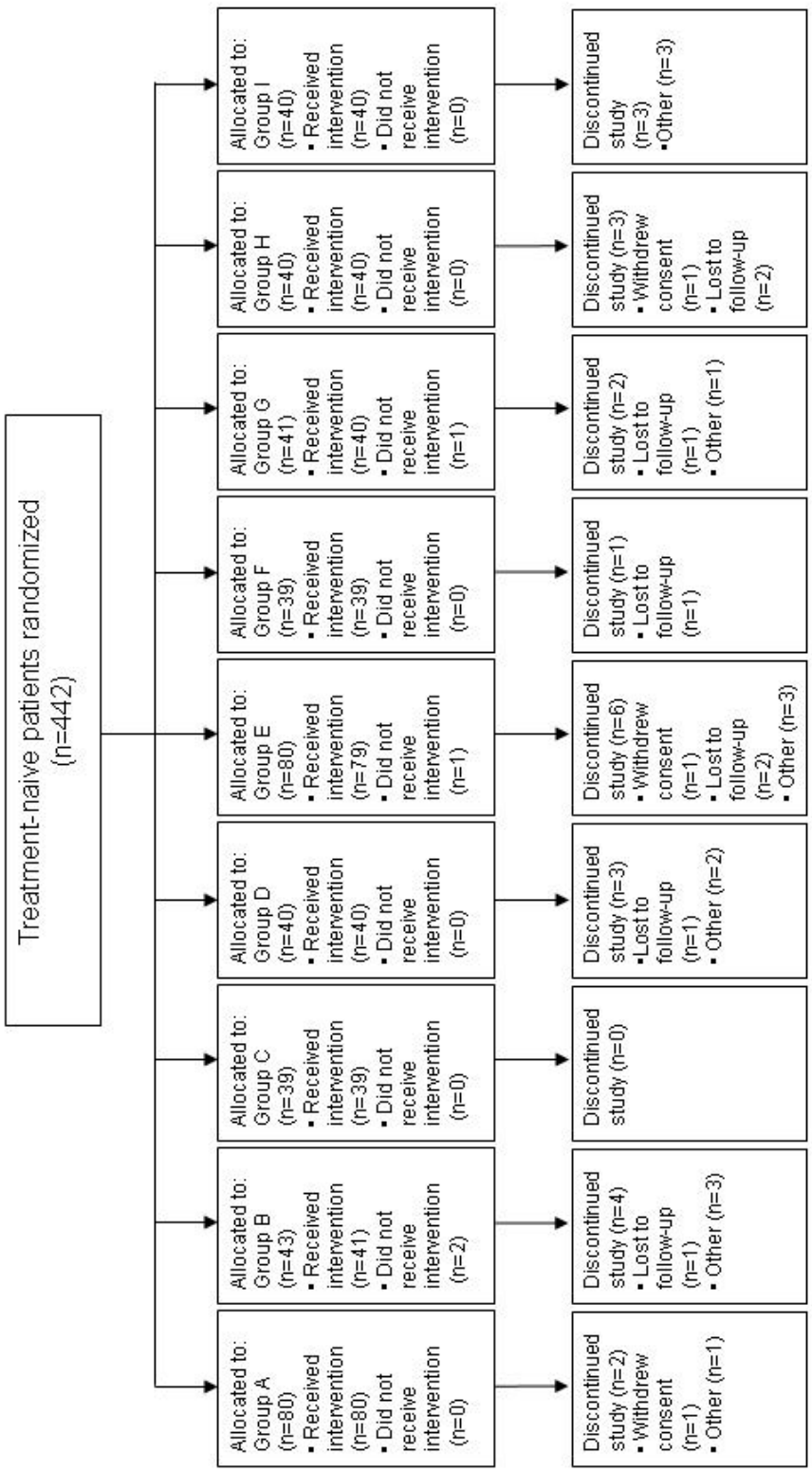

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Figure S1C.

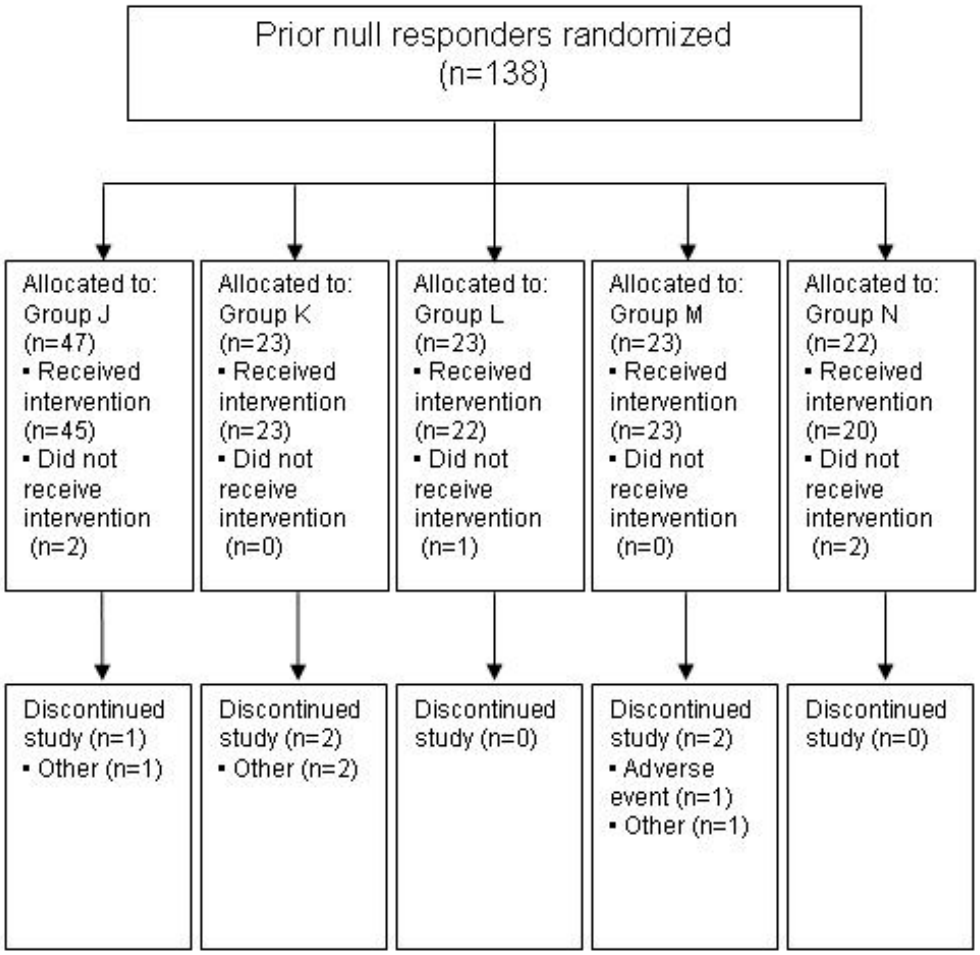

Figure S1. Patients were assessed for eligibility (S1A); treatment-naïve patients (S1B) and prior null responders (S1C) with chronic hepatitis C were randomized to receive a combination regimen of ABT-450/r with ABT-267, and/or ABT-333, and/or weight-based ribavirin. Duration of treatment was 8, 12, or 24 weeks. Follow-up was through 48 weeks post-treatment.

Table S1. Reasons for screen failure.

Screened patients failing to meet criteria	Inclusion criteria
4	Females must have negative results for pregnancy tests performed: • At Screening on a serum specimen obtained within 35 days prior to initial study drug administration, and • On a urine sample obtained on Study Day 1 (prior to dosing).
17	Subject must meet one of the following: • Treatment-naïve: Subject has never received antiviral treatment for hepatitis C infection, OR • Prior null responders: Subject has documentation that they previously received pegIFN plus ribavirin for at least 12 weeks and failed to achieve a 2 $\log_{10}$ HCV RNA decrease at Week 12. Subjects may be considered to meet this definition if the lack of treatment response was documented up to 2 weeks prior to treatment Week 12 with the approval of the Study Designated Physician.
6	Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.
5	Body mass index (BMI) is > 18 to < 38 kg/m^2. Body mass index is calculated as weight measured in kg divided by the square of height measured in meters (m).
2	Must voluntarily sign and date an informed consent, approved by an Institutional Review Board/Ethics Committee (IRB/EC), prior to the initiation of any screening or study-specific procedures.
57	Chronic HCV genotype 1-infection for at least 6 months prior to study enrollment. Chronic HCV infection is defined as one of the following: • Positive for anti-HCV antibody or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV antibody at the time of Screening; or • Positive for anti-HCV antibody 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).
95	Per local standard practice, documented results of: • Fibro Test score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2 at Screening, or • FibroScan® result of < 9.6 kPa, or • the absence of cirrhosis based on a liver biopsy within the last 36 months.
16	Subject has a plasma HCV RNA level > 50,000 International Units (IU)/mL at Screening.
Screened patients failing to meet criteria	**Exclusion Criteria**
4	History of severe, life-threatening or other significant sensitivity to any drug.
1	Use of any herbal supplements (including milk thistle) within the 2-week period prior to the first dose of study drug.
1	Females who are pregnant or breastfeeding or males whose partner is pregnant.
8	Recent (within 6-months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol.
3	Positive test result for hepatitis B surface antigen (HBsAg) or anti-HIV antibodies (anti-HIV Ab).
3	Use of known inhibitors (e.g., ketoconazole) or inducers (e.g., phenobarbital, rifampin, carbamazepine, St. John's Wort) of cytochrome P450 3A (CYP3A), cytochrome P450 2C8 (CYP2C8) (e.g., gemfibrozil, montelukast) and organic anion transporting polypeptide 1B1 (OATP1B1), (e.g., cyclosporine) within 1 month prior to study drug administration.
45	Positive result of a urine drug screen at the Screening Visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, and propoxyphene with the exception of a positive result (including methadone), associated with documented short-term

	use or chronic stable use of a prescribed medication in that class.
11	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 subject an unsuitable candidate for this study in the opinion of the Investigator.
19	History of uncontrolled seizures, cancer (except basal cell carcinoma of the skin), or uncontrolled diabetes, as defined by a hemoglobin A1C level > 8.0%. 11. Any current or past clinical evidence of cirrhosis (e.g., ascites, esophageal varices), or a liver biopsy showing cirrhosis.
8	Any current or past clinical evidence of cirrhosis (e.g., ascites, esophageal varices), or a liver biopsy showing cirrhosis.
106	Screening laboratory analyses show any of the following abnormal laboratory results: • Alanine aminotransferase (ALT) > 5 X upper limit of normal (ULN), • Aspartate aminotransferase (AST) > 5 X ULN, • Calculated creatinine clearance (using Cockcroft-Gault method) < 50 mL/min, • Albumin < lower limit of normal (LLN), • Prothrombin time INR > 1.5, • Hemoglobin < LLN, • Platelets < 120,000 cells per mm^3 for subjects with METAVIR score < 3 or Ishak score < 4 on a biopsy within the last 3 years; f for subjects with METAVIR score of 3 or Ishak score of 4, platelets < LLN, • Absolute neutrophil count < 1500 cells/µL, • Total bilirubin > 1.5 mg/dL, • HCV RNA levels that are above the level of assay quantification.
19	Clinically significant abnormal ECG or ECG with QTc using Fridericia's correction formula (QTcF) > 450 msec at Screening or Day 1 (prior to dosing).
1	Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks prior to study drug administration.
1	Consideration by the Investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-450, ABT-267, ABT-333, ritonavir, or ribavirin.
4	Current enrollment in another clinical study or previous use of any investigational or commercially available anti-HCV agents including previous exposure to ABT-450, ABT-267, ABT-333, ritonavir.
Screened patients who met eligibility criteria but failed screening for other reasons	**Reason for exclusion**
25	Declined to participate
1	Lost to follow-up
45	Other

Note: Some subjects failed screening due to multiple reasons

Table S2. Baseline patient characteristics: Treatment-naïve patients.*

	Treatment-naïve Patients								
Subgroup	A	B	C	D	E	F	G	H	I
N	80	41	39	40	79	39	40	40	40
Treatment duration	8 weeks	12 weeks						24 weeks	
Drug combination	450/r + 267 + 333 + ribavirin	450/r + 333 + ribavirin	450/r + 267 + ribavirin	450/r + 267 + ribavirin	450/r + 267 + 333	450/r + 267 + 333 + ribavirin	450/r + 267 + 333 + ribavirin	450/r + 267 + 333 + ribavirin	450/r + 267 + 333 + ribavirin
ABT-450/r dose	150/100mg	150/100mg	100/100mg	200/100mg	150/100mg	100/100mg	150/100mg	100/100mg	150/100mg
Male sex- no. (%)	46 (58)	18 (44)	25 (64)	20 (50)	45 (57)	20 (51)	24 (60)	18 (45)	16 (40)
Age- yr	50.1±9.99	50.8±9.84	51.1±8.07	49.0±10.59	48.3±10.53	49.4±9.72	51.0±11.08	51.5±11.95	51.5±9.78
Race†, Black - no. (%)	9 (11)	5 (12)	8 (21)	8 (20)	13 (17)	8 (21)	5 (13)	2 (5)	2 (5)
Ethnicity†, Latino - no. (%)	5 (6)	4 (10)	3 (8)	3 (8)	7 (9)	3 (8)	3 (8)	4 (10)	1 (3)
HCV subtype, 1a - no. (%)	56 (70)	29 (71)	26 (67)	26 (65)	52 (67)	27 (69)	27 (68)	27 (68)	27 (68)
IL28B genotype, non-CC - no. (%)	58 (73)	27 (66)	29 (74)	29 (73)	56 (71)	28 (72)	29 (73)	29 (73)	29 (73)
BL HOMA-IR ≥3 – no. (%)	16 (22)	6 (17)	7 (21)	12 (32)	19 (29)	11 (31)	14 (39)	7 (21)	6 (17)
BL IP-10 ≥600 ng/L - no. (%)	16 (22)	8 (20)	11 (28)	14 (35)	15 (20)	11 (28)	6 (15)	9 (23)	11 (28)
Fibrosis score ≥F2‡ - no. (%)	30 (38)	11 (27)	6 (15)	16 (40)	20 (25)	14 (36)	11 (28)	10 (25)	9 (23)
HCV RNA Mean $\log_{10}$ level- IU/mL	6.60±0.58	6.60±0.53	6.47±0.52	6.48±0.63	6.49±0.51	6.56±0.51	6.36±0.66	6.56±0.51	6.56±0.54

*Plus-minus values are means ±SD. Differences in baseline characteristics among treatment subgroups within the cohort of previously untreated patients were calculated with the use of chi-square tests for categorical data and one-way analysis of variance for continuous data. There were no significant differences among the treatment subgroups in the cohort of previously untreated patients for any characteristic (P>0.05 for all comparisons).

†Race and ethnicity were self-reported.

‡A fibrosis score was determined by liver biopsy (Metavir or Ishak score), FibroScan, or FibroTest. Details of scoring are in Table S4 of the Supplementary Appendix.

Table S3. Baseline patient characteristics: Prior null responders.*

	Prior Null Responders				
Subgroup	J	K	L	M	N
N	45	23	22	23	20
Treatment duration	12 weeks			24 weeks	
Drug combination	450/r + 267 + ribavirin	450/r + 267 + 333 + ribavirin	450/r + 267 + 333 + ribavirin	450/r + 267 + 333 + ribavirin	450/r + 267 + 333 + ribavirin
ABT-450/r dose	200/100mg	100/100mg	150/100mg	100/100mg	150/100mg
Baseline Characteristic					
Male sex- no. (%)	27 (60)	16 (70)	12 (55)	15 (65)	12 (60)
Age- yr	50.6±11.19	48.5±12.91	51.2±12.07	51.5±9.06	54.6±11.78
Race†, Black- no. (%)	9 (20)	4 (17)	2 (9)	0	3 (15)
Ethnicity†, Latino- no. (%)	5 (11)	2 (9)	2 (9)	3 (13)	1 (5)
HCV subtype, 1a- no. (%)	26 (58)	15 (65)	13 (59)	14 (61)	13 (65)
IL28B genotype, non-CC -no. (%)	44 (98)	22 (96)	21 (95)	22 (96)	20 (100)
BL HOMA-IR ≥3 – no. (%)	11 (29)	8 (42)	6 (30)	2 (11)	7 (44)
BL IP-10 ≥600 ng/L- no. (%)	18 (42)	10 (46)	8 (36)	8 (36)	9 (47)
Fibrosis score ≥F2‡- no. (%)	20 (44)	8 (35)	9 (41)	15 (65)	14 (70)
HCV RNA Mean $\log_{10}$ level- IU/mL	6.58±0.50	6.68±0.41	6.41±0.47	6.85±0.28	6.74±0.45

*Plus-minus values are means ±SD. Differences in baseline characteristics among treatment subgroups within the cohort of patients who had not had a response to prior therapy were calculated with the use of chi-square tests for categorical data and one-way analysis of variance for continuous data. The fibrosis score and hepatitis C virus (HCV) RNA level differed significantly among the treatment subgroups in the cohort of patients who had not had a response to prior therapy (P = 0.01 and 0.02, respectively).

†Race and ethnicity were self-reported.

‡A fibrosis score was determined by liver biopsy (Metavir or Ishak score), FibroScan, or FibroTest. Details of scoring are in Table S4 of the Supplementary Appendix.

Table S4. Fibrosis scoring*.

Fibrosis score	Liver biopsy (Metavir)	Liver biopsy (Ishak)	FibroScan	Fibro Test
F0-F1	0-1	0-2	0.0-<8.8 KPA	0.00-0.48
F2	2	3	8.8-<9.6 KPA	0.49-0.58
F3	3	4	9.6-<14.6 KPA	0.59-0.72
F4	4	5-6	≥14.6 KPA	≥0.73

*If there were multiple assessments on the same date for a subject, fibrosis score was calculated in the order of liver biopsy, FibroScan, and Fibro Test. If there were assessments on different dates for a subject by different methods, fibrosis score was calculated in the order of liver biopsy, FibroScan, and Fibro Test. If there were assessments on different dates for a subject by the same method, fibrosis score was calculated by maximum value.

Table S5. SVR_{24}* Rates by Subgroup.

Cohort	Subgroup	Drug Combination	Duration (weeks)	SVR_{24}	
				no./ total no.	***% (95% CI)***
Treatment-Naïve Patients (N=438)	A	ABT-450/r 150/100 mg +ABT-267 + ABT-333 + ribavirin	8	70/80	87.5 (78-94)
	B	ABT-450/r 150/100 mg + ABT-333 + ribavirin	12	34/41	82.9 (68-93)
	C	ABT-450/r 100/100 mg + ABT-267 + ribavirin	12	33/39	84.6 (69-94)
	D	ABT-450/r 200/100 mg + ABT-267 + ribavirin	12	37/40	92.5 (80-98)
	E	ABT-450/r 150/100 mg + ABT-267 + ABT-333	12	70/79	88.6 (79-95)
	F	ABT-450/r 100/100 mg + ABT-267 + ABT-333 + ribavirin	12	38/39	97.4 (87-100)
	G	ABT-450/r 150/100 mg + ABT-267 + ABT-333 + ribavirin	12	38/40	95.0 (83-99)
	H	ABT-450/r 100/100 mg + ABT-267 + ABT-333 + ribavirin	24	37/40	92.5 (80-98)
	I	ABT-450/r 150/100 mg + ABT-267 + ABT-333 + ribavirin	24	36/40	90.0 (76-97)
Prior Null Responders (N=133)	J	ABT-450/r 200/100 mg + ABT-267 + ribavirin	12	40/45	88.9 (76-96)
	K	ABT-450/r 100/100 mg + ABT-267 + ABT-333 + ribavirin	12	21/23	91.3 (72-99)
	L	ABT-450/r 150/100 mg + ABT-267 + ABT-333 + ribavirin	12	21/22	95.5 (77-100)
	M	ABT-450/r 100/100 mg + ABT-267 + ABT-333 + ribavirin	24	21/23	91.3 (72-99)
	N	ABT-450/r 150/100 mg + ABT-267 + ABT-333 + ribavirin	24	20/20	100 (83-100)

*SVR_{24} is defined as HCV RNA <lower limit of quantitation (25 IU/mL) at post-treatment week 24.

Table S6. Primary and secondary endpoint comparisons.

Comparison (Description)	Comparison (Groups)	SVR_{24}		Logistic regression		Strata-adjusted MH	
		First grouping, n/N (%)	Second grouping, n/N (%)	Odds Ratio, (95% CI)	*P*-value	Difference, (95% CI)	*P*-value
Treatment-naïve 3 agents + ribavirin 8 weeks Versus Treatment-naïve 3 agents + ribavirin (ABT-450/r dose 150/100mg)* 12 weeks	A versus G	70/80 (87.5)	38/40 (95.0)	0.49 (0.09, 2.61)	0.41	-7.30 (-19.43, 4.83)	0.24
Treatment-naïve 3 agents + ribavirin 8 weeks Versus Treatment-naïve 3 agents + ribavirin 12 weeks	A versus (F+G)	70/80 (87.5)	76/79 (96.2)	0.32 (0.08, 1.25)	0.10	-8.57 (-18.00, 0.86)	0.08
Treatment-naïve 3 agents + ribavirin 8 weeks Versus Treatment-naïve and null responders 3 agents + ribavirin 12 weeks	A versus (F+G+K+L)	70/80 (87.5)	118/124 (95.2)	0.35 (0.12, 1.08)	0.07	-7.77 (-16.68, 1.14)	0.09
Treatment-naïve 3 agents + ribavirin 8 weeks Versus Treatment-naïve and null responders 3 agents + ribavirin 24 weeks	A versus (H+I+M+N)	70/80 (87.5)	114/123 (92.7)	0.62 (0.23, 1.64)	0.33	-4.29 (-13.69, 5.12)	0.37

Table S6. Primary and secondary endpoint comparisons (Continued).

Comparison (Description)	Comparison (Groups)	SVR_{24}		Logistic regression		Strata-adjusted MH	
		First grouping, n/N (%)	Second grouping, n/N (%)	Odds Ratio, (95% CI)	*P*-value	Difference, (95% CI)	*P*-value
Treatment-naïve and null responders 3 agents + ribavirin 12 weeks Versus Treatment-naïve and null responders 3 agents + ribavirin 24 weeks	(F+G+K+L) versus (H+I+M+N)	118/124 (95.2)	114/123 (92.7)	1.61 (0.54, 4.79)	0.39	2.55 (-3.89, 8.99)	0.44
Treatment-naive ABT-450/r + ABT-333 + ribavirin 12 weeks Versus Treatment-naïve and null responders 3 agents + ribavirin 12 weeks	B versus (F+G+K+L)	34/41 (82.9)	118/124 (95.2)	NA	-	-12.16 (-25.20, 0.88)	0.07
Treatment-naïve ABT-450/r + ABT-333 + ABT-267 12 weeks Versus Treatment-naïve and null responders 3 DAA + RBV 12 weeks	E versus (F+G+K+L)	70/79 (88.6)	118/124 (95.2)	NA	-	-7.13 (-15.77, 1.51)	0.11
Treatment–naïve and null responder ABT-450/r + ABT-267 + RBV 12 weeks Versus Treatment-naïve and null responders 3 DAA + RBV 12 weeks	(C+D+J) versus (F+G+K+L)	110/124 (88.7)	118/124 (95.2)	NA	-	-6.75 (-13.93, 0.43)	0.07

Table S6. Primary and secondary endpoint comparisons (Continued).

Comparison (Description)	Comparison (Groups)	SVR_{24}		Logistic regression		Strata-adjusted MH	
		First grouping, n/N (%)	Second grouping, n/N (%)	Odds Ratio, (95% CI)	*P*-value	Difference, (95% CI)	*P*-value
Treatment-naïve 3 DAA + RBV 12 weeks Versus Null responder 3 DAA + RBV 12 weeks	(F+G) versus (K+L)	76/79 (96.2)	42/45 (93.3)	NA	-	2.30 (-9.07, 13.67)	0.70
Treatment-naïve 3 agents + ribavirin 24 weeks Versus Null responder 3 agents + ribavirin 24 weeks	(H+I) versus (M+N)	73/80 (91.3)	41/43 (95.3)	1.86 (0.22, 16.11)	0.57	-0.11 (-9.47, 9.26)	0.98
Treatment-naïve 3 agents + ribavirin 12 and 24 weeks Versus Null responder 3 agents + ribavirin 12 and 24 weeks	(F+G+H+I) versus (K+L+M+N)	149/159 (93.7)	83/88 (94.3)	1.40 (0.37, 5.30)	0.62	0.78 (-6.18, 7.74)	0.83

*Groups differing in ABT-450/r dose only are combined in all other relevant comparisons
Logistic regression with baseline $\log_{10}$ HCV RNA level, treatment group, IL28B genotype (CC or non-CC), HCV subgenotype (1a or non-1a), and geographic region (US or non-US) as predictors.
Stratum-adjusted MH method with IL28B genotype (CC or non-CC) and HCV subgenotype (1a or non-1a)
MH=Mantel-Haenszel
SVR_{24} = Sustained virologic response (HCV RNA <25 IU/mL) at post-treatment week 24, with no confirmed virologic rebound or post-treatment relapse.
NA = Not available due to separation or quasi-separation in logistic regression.

Table S7. SVR_{24}* rates by subpopulations: Treatment-naïve patients.

	Treatment-naïve Patients											
Group	1		2		3		4		5		6	
N	80		41		79		79		79		80	
Treatment duration	8-weeks		12-weeks								24-weeks	
Drug Combination	450/r + 267 + 333 + ribavirin		450/r + 333 + ribavirin		450/r + 267 + ribavirin		450/r + 267 + 333		450/r + 267 + 333 + ribavirin		450/r + 267 + 333 + ribavirin	
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
IL28B CC	20/22	91 (71-99)	11/14	79 (49-95)	20/21	95 (76-100)	21/23	91 (72-99)	22/22	100 (85-100)	17/22	77 (55-92)
IL28B CT	37/41	90 (77-97)	15/18	83 (59-96)	37/45	82 (68-92)	36/39	92 (79-98)	37/39	95 (83-99)	44/46	96 (85-99)
IL28B TT	13/17	77 (50-93)	8/9	89 (52-100)	13/13	100 (75-100)	13/17	77 (50-93)	17/18	94 (73-100)	12/12	100 (74-100)
Genotype 1a	47/56	84 (72-92)	22/29	76 (56-90)	43/52	83 (70-92)	43/52	83 (70-92)	51/54	94 (85-99)	48/54	89 (77-96)
Genotype 1b	23/24	96 (79-100)	12/12	100 (74-100)	27/27	100 (87-100)	25/25	100 (86-100)	25/25	100 (86-100)	24/25	96 (80-100)
Black	7/9	78 (40-97)	4/5	80 (28-99)	14/16	88 (62-98)	13/13	100 (75-100)	13/13	100 (75-100)	3/4	75 (19-99)
Non-black	63/71	89 (79-95)	30/36	83 (67-94)	56/63	89 (78-95)	57/66	86 (76-94)	63/66	96 (87-99)	70/76	92 (84-97)
Baseline viral load $\geq$800,000 IU/mL	61/71	86 (76-93)	30/36	83 (67-94)	58/67	87 (76-94)	62/70	89 (79-95)	63/65	97 (89-100)	64/70	91 (82-97)
Baseline viral load <800,000 IU/mL	9/9	100 (66-100)	4/5	80 (28-99)	12/12	100 (74-100)	8/9	89 (52-100)	13/14	93 (66-100)	9/10	90 (55-100)

*SVR_{24} is defined as HCV RNA <lower limit of quantitation (25 IU/mL) at post-treatment week 24.

Table S8. SVR_{24}* rates by subpopulations: Prior null responders.

	Prior Null Responders					
Group	7		8		9	
N	45		45		43	
Treatment duration	12-weeks				24-weeks	
Drug Combination	450/r + 267 + ribavirin		450/r + 267 + 333 + ribavirin		450/r + 267 + 333 + ribavirin	
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
IL28B CC	1/1	100 (3-100)	2/2	100 (16-100)	1/1	100 (3-100)
IL28B CT	24/28	86 (67-96)	25/28	89 (72-98)	24/25	96 (80-100)
IL28B TT	15/16	94 (70-100)	15/15	100 (78-100)	16/17	94 (71-100)
Genotype 1a	21/26	81 (61-93)	25/28	89 (72-98)	26/27	96 (81-100)
Genotype 1b	19/19	100 (82-100)	17/17	100 (80-100)	15/16	94 (70-100)
Black	8/9	89 (52-100)	6/6	100 (54-100)	3/3	100 (29-100)
Non-black	32/36	89 (74-97)	36/39	92 (79-98)	38/40	95 (83-99)
Baseline viral load $\geq$800,000 IU/mL	37/42	88 (74-96)	40/43	93 (81-99)	40/42	95 (84-99)
Baseline viral load <800,000 IU/mL	3/3	100 (29-100)	2/2	100 (16-100)	1/1	100 (3-100)

*SVR_{24} is defined as HCV RNA <lower limit of quantitation (25 IU/mL) at post-treatment week 24.

Table S9. Virologic response: Treatment-naïve patients.

	Treatment-naïve Patients											
Group	1		2		3		4		5		6	
N	80		41		79		79		79		80	
Treatment duration	8-weeks		12-weeks								24-weeks	
Drug Combination	450/r + 267 + 333 + ribavirin		450/r + 333 + ribavirin		450/r + 267 + ribavirin		450/r + 267 + 333		450/r + 267 + 333 + ribavirin		450/r + 267 + 333 + ribavirin	
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Breakthrough	0/80	-	1/41	2 (0-13)	1/79	1 (0-7)	1/79	1 (0-7)	0/79	-	0/80	-
Relapse by post-treatment week 12	9/80	11 (5-20)	4/40	10 (3-24)	5/78	6 (2-14)	5/78	6 (2-14)	1/79	1 (0-7)	2/80	3 (0-9)
Relapse at post-treatment week 24	1/80	1 (0-7)	0	-	2/78	3 (0-9)	0	-	0	-	0	-
Non-virologic failure by post-treatment week 12*	0	-	1/41	2 (0-13)	1[§]/79	1 (0-7)	1/79	1 (0-7)	0	-	4/80	5 (1-12)
Non-virologic failure at post-treatment week 24*	0	-	1/41	2 (0-13)	0	-	2/79	3 (0-9)	2/79	3 (0-9)	1/80	1 (0-7)
SVR_{12}[†]	71/80	89 (80-95)	35/41	85 (71-94)	72/79	91 (83-96)	72/79	91 (83-96)	78/79	99 (93-100)	74/80	93 (84-97
SVR_{24}[‡]	70/80	88 (78-94)	34/41	83 (68-93)	70/79	89 (79-95)	70/79	89 (79-95)	76/79	96 (89-99)	73/80	91 (83-96)

*Reasons for non-virologic failure included lost to follow-up and withdrew consent.
[†]SVR_{12} is defined as HCV RNA <lower limit of quantitation (25 IU/mL) at post-treatment week 12.
[‡]SVR_{24} is defined as HCV RNA <lower limit of quantitation (25 IU/mL) at post-treatment week 24.
[§]This patient received 9 days of study drug and had HCV RNA <lower limit of quantitation (25 IU/mL) at the end of treatment. This patient returned at post-treatment week 48 with HCV RNA >lower limit of quantitation (25 IU/mL).

Table S10. Virologic response: Prior null responders.

	Prior Null Responders					
Group	7		8		9	
N	45		45		43	
Treatment duration	12-weeks				24-weeks	
Drug Combination	450/r + 267 + ribavirin		450/r + 267 + 333 + ribavirin		450/r + 267 + 333 + ribavirin	
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Breakthrough	0/45	-	3/45	7 (1-18)	1/43	2 (0-12)
Relapse by post-treatment week 12	5/45	11 (4-24)	0	-	0	-
Relapse at post-treatment week 24	0	-	0	-	0	-
Non-virologic failure by post-treatment week 12*	0	-	0	-	0	-
Non-virologic failure at post-treatment week 24*	0	-	0	-	1/43	2 (0-12)
SVR_{12}[†]	40/45	89 (76-96)	42/45	93 (82-99)	42/43	98 (88-100)
SVR_{24}[‡]	40/45	89 (76-96)	42/45	93 (82-99)	41/43	95 (84-99)

*Reasons for non-virologic failure included lost to follow-up and withdrew consent.
[†]SVR_{12} is defined as HCV RNA <lower limit of quantitation (25 IU/mL) at post-treatment week 12.
[‡]SVR_{24} is defined as HCV RNA <lower limit of quantitation (25 IU/mL) at post-treatment week 24.

Table S11. SVR_{24} by subpopulations within each cohort (all subjects)

	Cohort 1: Treatment-naïve Patients		Cohort 2: Prior Null Responders	
	Odds Ratio	**P Value**	**Odds Ratio**	**P Value**
IL28B CC vs. IL28B CT	0.912	0.803	*	*
IL28B CC vs. IL28B TT	1.123	0.794	*	*
Genotype 1a vs. Genotype 1b	0.087	0.0008	0.157	0.083
Black vs. Non-black	1.035	0.941	1.443	0.735
Baseline viral load ≥800,000 IU/mL vs. <800,000 IU/mL	0.600	0.347	†	†

* Not applicable as there is no failure in CC category.
† Not applicable as there is no failure in <800,000 category.
Five subpopulation comparisons were tested in each cohort. All are reported here.

Table S12. Treatment-emergent events occurring in >5% of patients in any subgroup.

Adverse event, no. (%)	A (N=80)	B (N=41)	C (N=39)	D (N=40)	E (N=79)	F (N=39)	G (N=40)	H (N=40)	I (N=40)
Blood and lymphatic system disorders									
Anemia	5(6.3)	1 (2.4)	2 (5.1)	1 (2.5)	1 (1.3)	3 (7.7)	4 (10.0)	4 (10.0)	2 (5.0)
Ear and labyrinth disorders									
Tinnitus	1 (1.3)	3 (7.3)	0	0	1 (1.3)	0	0	1 (2.5)	2 (5.0)
Gastrointestinal disorders									
Abdominal distention	0	1 (2.4)	1 (2.6)	0	3 (3.8)	2 (5.1)	1 (2.5)	3 (7.5)	2 (5.0)
Abdominal pain	1 (1.3)	3 (7.3)	1 (2.6)	3 (7.5)	3 (3.8)	1 (2.6)	2 (5.0)	4 (10.0)	3 (7.5)
Abdominal pain upper	0	2 (4.9)	2 (5.1)	3 (7.5)	3 (3.8)	3 (7.7)	1 (2.5)	2 (5.0)	2 (5.0)
Cheilitis	0	0	2 (5.1)	0	0	0	0	0	0
Constipation	3 (3.8)	1 (2.4)	2 (5.1)	3 (7.5)	5 (6.3)	1 (2.6)	0	6 (15.0)	3 (7.5)
Diarrhea	8 (10.0)	10 (24.4)	3 (7.7)	5 (12.5)	13 (16.5)	4 (10.3)	6 (15.0)	6 (15.0)	5 (12.5)
Dry mouth	4 (5.0)	0	1 (2.6)	1 (2.5)	2 (2.5)	1 (2.6)	0	1 (2.5)	1 (2.5)
Dyspepsia	7 (8.8)	1 (2.4)	5 (12.8)	4 (10.0)	2 (2.5)	0	4 (10.0)	3 (7.5)	3 (7.5)
Flatulence	0	1 (2.4)	1 (2.6)	3 (7.5)	4 (5.1)	1 (2.6)	1 (2.5)	0	1 (2.5)
Gastroesophageal reflux disease	1 (1.3)	0	0	2 (5.0)	3 (3.8)	0	2 (5.0)	1 (2.5)	1 (2.5)
Nausea	12 (15.0)	7 (17.1)	7 (17.9)	9 (22.5)	11 (13.9)	8 (20.5)	11 (27.5)	11 (27.5)	9 (22.5)
Toothache	1 (1.3)	0	0	0	1 (1.3)	0	0	3 (7.5)	0
Vomiting	7 (8.8)	4 (9.8)	1 (2.6)	3 (7.5)	4 (5.1)	3 (7.7)	1 (2.5)	3 (7.5)	1 (2.5)
General disorders and administration site conditions									
Asthenia	7 (8.8)	1 (2.4)	2 (5.1)	6 (15.0)	5 (6.3)	1 (2.6)	2 (5.0)	5 (12.5)	7 (17.5)
Chest pain	0	1 (2.4)	1 (2.6)	1 (2.5)	0	0	1 (2.5)	3 (7.5)	1 (2.5)
Chills	4 (5.0)	1 (2.4)	0	1 (2.5)	1 (1.3)	1 (2.6)	0	0	3 (7.5)
Fatigue	29 (36.3)	13 (31.7)	7 (17.9)	15 (37.5)	16 (20.3)	12 (30.8)	10 (25.0)	17 (42.5)	13 (32.5)
Feeling abnormal	2 (2.5)	1 (2.4)	0	0	0	1 (2.6)	1 (2.5)	0	1 (2.5)
Influenza like illness	0	2 (4.9)	2 (5.1)	1 (2.5)	0	0	1 (2.5)	0	0
Irritability	1 (1.3)	4 (9.8)	3 (7.7)	2 (5.0)	5 (6.3)	0	1 (2.5)	4 (10.0)	6 (15.0)
Edema peripheral	0	1 (2.4)	2 (5.1)	0	2 (2.5)	1 (2.6)	0	1 (2.5)	2 (5.0)
Pain	1 (1.3)	0	1 (2.6)	0	0	0	2 (5.0)	0	1 (2.5)
Pyrexia	1 (1.3)	1 (2.4)	1 (2.6)	2 (5.0)	2 (2.5)	1 (2.6)	1 (2.5)	2 (5.0)	0
Hepatobiliary disorders									
Jaundice	3 (3.8)	0	0	1 (2.5)	0	1 (2.6)	2 (5.0)	1 (2.5)	2 (5.0)
Immune system disorders									
Seasonal allergy	0	0	0	2 (5.0)	0	0	0	0	0

Table S12. Treatment-emergent events occurring in >5% of patients in any subgroup. (Continued)

Adverse event, no. (%)	A (N=80)	B (N=41)	C (N=39)	D (N=40)	E (N=79)	F (N=39)	G (N=40)	H (N=40)	I (N=40)
Infections and infestations									
Bronchitis	1 (1.3)	1 (2.4)	0	1 (2.5)	2 (2.5)	1 (2.6)	1 (2.5)	2 (5.0)	1 (2.5)
Herpes simplex	2 (2.5)	1 (2.4)	1 (2.6)	1 (2.5)	0	0	0	0	0
Influenza	1 (1.3)	0	0	1 (2.5)	2 (2.5)	1 (2.6)	0	0	1 (2.5)
Nasopharyngitis	4 (5.0)	3 (7.3)	1 (2.6)	3 (7.5)	8 (10.1)	1 (2.6)	6 (15.0)	4 (10.0)	2 (5.0)
Oral herpes	2 (2.5)	0	1 (2.6)	1 (2.5)	2 (2.5)	1 (2.6)	0	1 (2.5)	2 (5.0)
Rhinitis	1 (1.3)	0	2 (5.1)	3 (7.5)	2 (2.5)	0	0	0	0
Sinusitis	4 (5.0)	0	4 (10.3)	3 (7.5)	2 (2.5)	3 (7.7)	2 (5.0)	1 (2.5)	2 (5.0)
Subcutaneous abscess	0	0	0	0	0	2 (5.1)	0	1 (2.5)	0
Tooth infection	2 (2.5)	0	0	0	1 (1.3)	2 (5.1)	2 (5.0)	3 (7.5)	1 (2.5)
Upper respiratory tract infection	5 (6.3)	1 (2.4)	2 (5.1)	3 (7.5)	5 (6.3)	3 (7.7)	1 (2.5)	4 (10.0)	1 (2.5)
Urinary tract infection	4 (5.0)	3 (7.3)	2 (5.1)	0	1 (1.3)	0	0	4 (10.0)	2 (5.0)
Investigations									
Alanine aminotransferase increased	0	0	0	3 (7.5)	0	0	1 (2.5)	0	0
Blood bilirubin increased	1 (1.3)	0	0	1 (2.5)	0	2 (5.1)	1 (2.5)	0	0
Blood glucose increased	0	0	0	0	0	2 (5.1)	0	0	0
Hemoglobin decreased	0	0	0	0	1 (1.3)	1 (2.6)	0	0	0
Heart rate increased	0	0	1 (2.6)	0	0	2 (5.1)	1 (2.5)	1 (2.5)	0
Metabolism and nutrition disorders									
Decreased appetite	8 (10.0)	1 (2.4)	3 (7.7)	2 (5.0)	3 (3.8)	0	3 (7.5)	4 (10.0)	2 (5.0)
Musculoskeletal and connective tissue disorders									
Arthralgia	2 (2.5)	2 (4.9)	3 (7.7)	3 (7.5)	7 (8.9)	4 (10.3)	1 (2.5)	4 (10.0)	5 (12.5)
Back pain	2 (2.5)	1 (2.4)	0	3 (7.5)	4 (5.1)	2 (5.1)	0	4 (10.0)	1 (2.5)
Muscle spasms	2 (2.5)	1 (2.4)	1 (2.6)	1 (2.5)	1 (1.3)	2 (5.1)	3 (7.5)	2 (5.0)	0
Muscular weakness	2 (2.5)	1 (2.4)	3 (7.7)	0	0	1 (2.6)	0	0	0
Musculoskeletal pain	0	0	1 (2.6)	1 (2.5)	1 (1.3)	0	1 (2.5)	1 (2.5)	0
Myalgia	4 (5.0)	3 (7.3)	3 (7.7)	2 (5.0)	2 (2.5)	2 (5.1)	1 (2.5)	4 (10.0)	5 (12.5)
Pain in extremity	2 (2.5)	1 (2.4)	1 (2.6)	0	1 (1.3)	0	0	1 (2.5)	2 (5.0)

Table S12. Treatment-emergent events occurring in >5% of patients in any subgroup. (Continued)

Adverse event, no. (%)	A (N=80)	B (N=41)	C (N=39)	D (N=40)	E (N=79)	F (N=39)	G (N=40)	H (N=40)	I (N=40)
Nervous system disorders									
Disturbance in attention	2 (2.5)	1 (2.4)	1 (2.6)	1 (2.5)	1 (1.3)	0	2 (5.0)	6 (15.0)	3 (7.5)
Dizziness	5 (6.3)	7 (17.1)	2 (5.1)	0	4 (5.1)	3 (7.7)	0	5 (12.5)	3 (7.5)
Dysgeusia	2 (2.5)	1 (2.4)	3 (7.7)	0	2 (2.5)	1 (2.6)	2 (5.0)	1 (2.5)	3 (7.5)
Headache	28 (35.0)	13 (31.7)	13 (33.3)	10 (25.0)	15 (19.0)	14 (35.9)	7 (17.5)	13 (32.5)	16 (40.0)
Lethargy	0	0	0	2 (5.0)	1 (1.3)	0	0	0	1 (2.5)
Memory impairment	0	0	1 (2.6)	0	3 (3.8)	0	0	4 (10.0)	1 (2.5)
Paraesthesia	0	0	2 (5.1)	1 (2.5)	1 (1.3)	1 (2.6)	0	1 (2.5)	1 (2.5)
Psychiatric disorders									
Abnormal dreams	1 (1.3)	2 (4.9)	1 (2.6)	1 (2.5)	1 (1.3)	0	1 (2.5)	3 (7.5)	2 (5.0)
Anxiety	2 (2.5)	2 (4.9)	0	0	3 (3.8)	1 (2.6)	3 (7.5)	1 (2.5)	5 (12.5)
Depressed mood	1 (1.3)	3 (7.3)	0	1 (2.5)	0	0	0	0	0
Depression	3 (3.8)	3 (7.3)	2 (5.1)	1 (2.5)	1 (1.3)	2 (5.1)	1 (2.5)	7 (17.5)	5 (12.5)
Insomnia	10 (12.5)	8 (19.5)	7 (17.9)	2 (5.0)	6 (7.6)	6 (15.4)	10 (25.0)	8 (20.0)	12 (30.0)
Sleep disorder	1 (1.3)	0	0	0	0	0	0	1 (2.5)	1 (2.5)
Renal and urinary disorders									
Dysuria	0	0	0	0	0	1 (2.6)	1 (2.5)	0	0
Pollakiuria	0	0	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders									
Cough	12 (15.0)	5 (12.2)	6 (15.4)	5 (12.5)	2 (2.5)	1 (2.6)	7 (17.5)	8 (20.0)	4 (10.0)
Dyspnea	8 (10.0)	3 (7.3)	3 (7.7)	1 (2.5)	1 (1.3)	2 (5.1)	3 (7.5)	4 (10.0)	4 (10.0)
Dyspnea exertional	2 (2.5)	0	2 (5.1)	1 (2.5)	0	2 (5.1)	2 (5.0)	4 (10.0)	5 (12.5)
Oropharyngeal pain	3 (3.8)	0	2 (5.1)	2 (5.0)	0	1 (2.6)	0	1 (2.5)	3 (7.5)
Rhinorrhoea	1 (1.3)	0	0	0	0	0	0	1 (2.5)	0
Skin and subcutaneous tissue disorders									
Alopecia	0	0	0	0	2 (2.5)	0	0	2 (5.0)	4 (10.0)
Dry skin	4 (5.0)	3 (7.3)	0	3 (7.5)	1 (1.3)	3 (7.7)	1 (2.5)	3 (7.5)	3 (7.5)
Erythema	0	0	1 (2.6)	2 (5.0)	2 (2.5)	1 (2.6)	0	0	0
Pruritus	12 (15.0)	3 (7.3)	3 (7.7)	5 (12.5)	3 (3.8)	2 (5.1)	4 (10.0)	6 (15.0)	5 (12.5)
Pruritus generalized	2 (2.5)	5 (12.2)	0	0	1 (1.3)	0	4 (10.0)	1 (2.5)	2 (5.0)
Rash	10 (12.5)	2 (4.9)	3 (7.7)	3 (7.5)	6 (7.6)	5 (12.8)	6 (15.0)	8 (20.0)	6 (15.0)
Rash maculo-papular	1 (1.3)	1 (2.4)	3 (7.7)	0	1 (1.3)	0	0	0	0

Table S12. Treatment-emergent events occurring in >5% of patients in any subgroup. (Continued)

Adverse event, no. (%)	J (N=45)	K (N=23)	L (N=22)	M (N=23)	N (N=20)
Blood and lymphatic disorders					
Anemia	3 (6.7)	2 (8.7)	1 (4.5)	1 (4.3)	1 (5.0)
Ear and labyrinth disorders					
Tinnitus	0	0	0	0	0
Gastrointestinal disorders					
Abdominal distention	0	0	2 (9.1)	0	0
Abdominal pain	1 (2.2)	2 (8.7)	4 (18.2)	0	0
Abdominal pain upper	0	1 (4.3)	0	2 (8.7)	0
Cheilitis	0	0	0	0	0
Constipation	2 (4.4)	0	1 (4.5)	1 (4.3)	3 (15.0)
Diarrhea	7 (15.6)	5 (21.7)	3 (13.6)	5 (21.7)	3 (15.0)
Dry mouth	1 (2.2)	2 (8.7)	0	1 (4.3)	1 (5.0)
Dyspepsia	2 (4.4)	1 (4.3)	1 (4.5)	0	2 (10.0)
Flatulence	0	0	1 (4.5)	1 (4.3)	0
Gastroesophageal reflux disease	1 (2.2)	0	1 (4.5)	2 (8.7)	2 (10.0)
Nausea	6 (13.3)	5 (21.7)	4 (18.2)	4 (17.4)	4 (20.0)
Toothache	0	0	1 (4.5)	0	0
Vomiting	4 (8.9)	2 (8.7)	2 (9.1)	3 (13.0)	0
General disorders and administration site conditions					
Asthenia	10 (22.2)	1 (4.3)	3 (13.6)	2 (8.7)	2 (10.0)
Chest pain	1 (2.2)	2 (8.7)	1 (4.5)	0	0
Chills	1 (2.2)	0	0	1 (4.3)	1 (5.0)
Fatigue	12 (26.7)	7 (30.4)	5 (22.7)	6 (26.1)	3 (15.0)
Feeling abnormal	1 (2.2)	2 (8.7)	0	1 (4.3)	0
Influenza like illness	1 (2.2)	1 (4.3)	0	0	0
Irritability	7 (15.6)	1 (4.3)	1 (4.5)	1 (4.3)	2 (10.0)
Edema peripheral	0	0	1 (4.5)	1 (4.3)	0
Pain	0	1 (4.3)	0	2 (8.7)	0
Pyrexia	2 (4.4)	1 (4.3)	0	2 (8.7)	0
Hepatobiliary disorders					
Jaundice	1 (2.2)	2 (8.7)	1 (4.5)	0	1 (5.0)
Immune system disorders					
Seasonal allergy	3 (6.7)	0	0	0	0

Table S12. Treatment-emergent events occurring in >5% of patients in any subgroup. (Continued)

Adverse event, no. (%)	J (N=45)	K (N=23)	L (N=22)	M (N=23)	N (N=20)
Infection and infestations					
Bronchitis	1 (2.2)	0	2 (9.1)	0	0
Herpes simplex	0	0	1 (4.5)	0	2 (10.0)
Influenza	1 (2.2)	1 (4.3)	2 (9.1)	0	0
Nasopharyngitis	2 (4.4)	2 (8.7)	2 (9.1)	1 (4.3)	2 (10.0)
Oral herpes	3 (6.7)	2 (8.7)	1 (4.5)	1 (4.3)	1 (5.0)
Rhinitis	0	1 (4.3)	0	0	0
Sinusitis	1 (2.2)	1 (4.3)	1 (4.5)	0	3 (15.0)
Subcutaneous abscess	0	0	0	0	0
Tooth infection	1 (2.2)	0	1 (4.5)	0	0
Upper respiratory tract infection	3 (6.7)	0	4 (18.2)	0	0
Urinary tract infection	2 (4.4)	1 (4.3)	2 (9.1)	2 (8.7)	0
Investigations					
Alanine aminotransferase increased	1 (2.2)	0	0	0	0
Blood bilirubin increased	0	0	0	0	0
Blood glucose increased	0	0	0	0	0
Hemoglobin decreased	0	1 (4.3)	0	2 (8.7)	2 (10.0)
Heart rate increased	0	0	0	0	0
Metabolism and nutrition disorders					
Decreased appetite	3 (6.7)	1 (4.3)	0	1 (4.3)	0
Musculoskeletal and connective tissue disorders					
Arthralgia	3 (6.7)	3 (13.0)	2 (9.1)	2 (8.7)	5 (25.0)
Back pain	2 (4.4)	2 (8.7)	0	2 (8.7)	2 (10.0)
Muscle spasms	2 (4.4)	0	0	0	0
Muscular weakness	1 (2.2)	0	0	1 (4.3)	0
Musculoskeletal pain	0	0	0	0	2 (10.0)
Myalgia	5 (11.1)	2 (8.7)	2 (9.1)	4 (17.4)	2 (10.0)
Pain in extremity	0	3 (13.0)	0	0	0

Table S12. Treatment-emergent events occurring in >5% of patients in any subgroup. (Continued)

Adverse event, no. (%)	J (N=45)	K (N=23)	L (N=22)	M (N=23)	N (N=20)
Nervous system disorders					
Disturbance in attention	3 (6.7)	1 (4.3)	2 (9.1)	1 (4.3)	2 (10.0)
Dizziness	4 (8.9)	1 (4.3)	0	2 (8.7)	2 (10.0)
Dysgeusia	0	1 (4.3)	3 (13.6)	1 (4.3)	3 (15.0)
Headache	15 (33.3)	5 (21.7)	8 (36.4)	9 (39.1)	5 (25.0)
Lethargy	1 (2.2)	2 (8.7)	1 (4.5)	1 (4.3)	1 (5.0)
Memory impairment	1 (2.2)	0	0	2 (8.7)	0
Paraesthesia	1 (2.2)	0	0	2 (8.7)	3 (15.0)
Psychiatric disorders					
Abnormal dreams	1 (2.2)	1 (4.3)	0	0	1 (5.0)
Anxiety	4 (8.9)	0	1 (4.5)	1 (4.3)	2 (10.0)
Depressed mood	0	1 (4.3)	1 (4.5)	1 (4.3)	0
Depression	2 (4.4)	3 (13.0)	2 (9.1)	1 (4.3)	0
Insomnia	8 (17.8)	4 (17.4)	2 (9.1)	3 (13.0)	4 (20.0)
Sleep disorder	0	1 (4.3)	3 (13.6)	2 (8.7)	0
Dysuria	0	0	0	2 (8.7)	0
Pollakiuria	1 (2.2)	2 (8.7)	0	0	0
Respiratory, thoracic and mediastinal disorders					
Cough	7 (15.6)	1 (4.3)	2 (9.1)	9 (39.1)	0
Dyspnea	4 (8.9)	1 (4.3)	2 (9.1)	3 (13.0)	0
Dyspnea exertional	0	0	0	0	2 (10.0)
Oropharyngeal pain	2 (4.4)	3 (13.0)	1 (4.5)	2 (8.7)	0
Rhinorrhoea	0	0	0	2 (8.7)	0
Skin and subcutaneous disorders					
Alopecia	0	0	0	3 (13.0)	1 (5.0)
Dry skin	6 (13.3)	4 (17.4)	0	2 (8.7)	2 (10.0)
Erythema	0	0	0	2 (8.7)	0
Pruritus	6 (13.3)	4 (17.4)	3 (13.6)	4 (17.4)	2 (10.0)
Pruritus generalized	5 (11.1)	0	0	1 (4.3)	0
Rash	2 (4.4)	1 (4.3)	3 (13.6)	4 (17.4)	2 (10.0)
Rash maculo-papular	0	1 (4.3)	0	0	0

Table S13. Serious events occurring >30 days post-treatment.

Serious adverse event	Relationship to study drug	Treatment subgroup
Lung neoplasm malignant	Not related	L
Cardiac arrest	Not related	M
Coronary artery stenosis*	Probably not related	E
Arteriosclerosis*	Probably not related	E
Chest pain†	Not related	C
Blood pressure increased†	Not related	C
Lower limb fracture	Not related	C
Substance-induced psychotic disorder	Not related	J
Overdose‡	Not related	F
Pneumonia aspiration‡	Not related	F
Acute myocardial infarction§	Not related	B
Cerebral haematoma§	Not related	B
Brain herniation§	Probably not related	B
Surgery with drainage of frontal and ethmoid sinus	Not related	K
Appendicitis	Not related	J
Acute myocardial infarction	Not related	E
Chest pain‖	Not related	A
Headache‖	Not related	A
Venous thrombosis	Not related	H
Abortion spontaneous	Not related	L

*Occurred in the same patient, †Occurred in the same patient, ‡Occurred in the same patient, §Occurred in the same patient, ‖Occurred in the same patient.
Two separate patients had acute myocardial infarction.