Supplementary Appendix

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

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ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis:
Supplementary Appendix

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

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Abbreviations and Definitions

ALT	alanine aminotransferase
AST	aspartate aminotransferase
CT	computed tomography
DAA	direct-acting antivirals
HCV	hepatitis C virus
INR	international normalized ratio
IRT	interactive response technology
LLOD	lower limit of detection
LLOQ	lower limit of quantitation
MRI	magnetic resonance imaging
pegIFN	pegylated interferon
RBV	ribavirin
SVR_{12}	sustained virologic response 12 weeks post-dosing
ULN	upper limit of normal

Treatment-naïve	Never received peginterferon/ribavirin for the treatment of HCV
Null responder	Received at least 12 weeks of peginterferon/ribavirin for the treatment of HCV and failed to achieve a 2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12; or received at least 4 weeks of peginterferon/ribavirin for the treatment of HCV and achieved a < 1 $\log_{10}$ IU/mL reduction in HCV RNA at Week 4 (≥ 25 days
Partial responder	Received at least 20 weeks of peginterferon/ribavirin for the treatment of HCV and achieved ≥ 2 $\log_{10}$ reduction in HCV RNA at week 12, but failed to achieve HCV RNA undetectable at the end of treatment
Prior relapser	Received at least 36 weeks of peginterferon/ribavirin 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

Eligibility Criteria

Main Inclusion

1. Male or female between 18 and 70 years of age, 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 directed by the local ribavirin label.
3. Sexually active males must be surgically sterile or have male partners only or if sexually active with female partner(s) of childbearing potential must agree to practice two effective forms of birth control (as outlined in the patient informed consent or other patient information documents) throughout the course of the study, starting with Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label.
4. Patient has never received antiviral treatment (including pegIFN/RBV) for hepatitis C infection (treatment-naïve patient), or patient must have documentation that they were adherent to prior pegIFN/RBV therapy and meet one of the following categories (treatment-experienced patient):
    - Null-responder:
        - 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
        - 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 ≥ 2 $\log_{10}$ 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.
        - HCV RNA levels that serve as documentation to support the type of prior non-response should have been 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.

5. Chronic HCV-infection 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).
6. Screening laboratory result indicating HCV genotype 1-infection.
7. Per local standard practice, documentation of cirrhosis by one of the following methods:
   - Previous histologic diagnosis on liver biopsy, e.g., Metavir Score of > 3 (including 3/4 or 3–4), Ishak score of > 4 or,
   - FibroScan score ≥ 14.6 kPa within 6 months of Screening or during the Screening Period.

   (Patients with a non-qualifying FibroScan result may only be enrolled if they have a qualifying liver biopsy performed during screening.)
8. Compensated cirrhosis defined as Child-Pugh score of <7 at Screening.
9. Patient has plasma HCV RNA level > 10,000 IU/mL at Screening.
10. Absence of hepatocellular carcinoma as indicated by a negative ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) performed within 3 months prior to Screening or a negative ultrasound 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 or anti-human immunodeficiency virus antibody.
3. HCV genotype performed during screening indicating unable to genotype or co-infection with any other HCV genotype.
4. Prior therapy with DAAs for the treatment of HCV, including telaprevir and boceprevir.
5. 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 Child-Pugh B or C Classification or clinical history of liver decompensation including ascites (noted on physical exam), variceal bleeding or hepatic encephalopathy.
7. Serum Alpha-Fetoprotein > 100 ng/mL at Screening.

8. A positive screening ultrasound for hepatocellular carcinoma confirmed with a subsequent CT scan or MRI during the screening period.
9. 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
    - 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.
10. Screening laboratory analyses showing any of the following abnormal laboratory results:
    - Alanine aminotransferase (ALT) > 7 × upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) > 7 × ULN
    - Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min
    - Albumin < 2.8 g/dL
    - International normalized ratio (INR) > 2.3. Patients with a known inherited blood disorder and INR > 2.3 may be enrolled with permission of the AbbVie Study Designated Physician
    - Hemoglobin < LLN
    - Platelets < 60,000 cells per mm^3
    - Absolute neutrophil count < 1500 cells/µL (< 1200 cells/µL for patients of black race or patients of African descent who are black)
    - Total bilirubin ≥ 3.0 mg/dL

Randomization Methods

Patients were stratified by having received previous pegIFN/RBV treatment (treatment-experienced) versus being treatment-naïve. The treatment-naïve patients were stratified by HCV subgenotype (1a versus non-1a) and by IL28B genotype (CC versus non-CC). The treatment-experienced patients were stratified by type of non-response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser, as defined in the inclusion criteria) and by HCV subgenotype (1a versus non-1a).

Per the original protocol, the first 200 patients were randomized in a 3:5 ratio to the 12 and 24 week arms, and the last 100 patients were to be randomized in a 3:1 ratio to the 12- and 24-week arms to achieve an overall randomization ratio of 1:1 to each arm.

An unanticipated increase in the planned number of patients evaluated at the end of the study screening period occurred. Given the limited therapeutic options available for patients with cirrhosis, all eligible patients were allowed to enroll and were randomized in the 3:1 ratio to the 12- and 24-week arms, resulting in a greater number of patients in the 12-week treatment arm than planned.

Collection of Samples for HCV Genotype and RNA Measurement

Plasma samples for HCV genotype and subgenotype were collected at screening. Genotype and subgenotype were assessed 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.

Plasma samples for determining HCV RNA levels were collected at screening and baseline visit, and for all patients at weeks 1, 2, 3, 4, 6, 8, and 12 of the study period, and for patients in the 24-week treatment arm at weeks 16, 20, and 24; samples were collected at premature discontinuation from the treatment period for patients in either treatment arm. In the post-treatment period, plasma samples for determining HCV RNA were collected at weeks 2, 4, 8, 12, 24, 36, and 48, or at premature discontinuation from the post-treatment period.

HCV RNA Measurement

Plasma HCV RNA levels were determined by the central laboratory for each sample collected, using the Roche COBAS® TaqMan® real-time reverse transcriptase-polymerase chain reaction assay v. 2.0. The lower limit of detection (LLOD) for this assay is 15 IU/mL and the lower limit of quantitation (LLOQ) is 25 IU/mL.

Virologic Failure Criteria

The following criteria were considered evidence of virologic failure. Patients demonstrating any of the following were to be discontinued from study drug:

- confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of > 1 log10 IU/mL above nadir) at any time point during treatment;
- failure to achieve HCV RNA < LLOQ by Week 6; or
- confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point after HCV RNA < LLOQ during treatment.

If any of the above criteria were met, the patient was to discontinue study treatment. Patients 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. Confirmation of an HCV RNA ≥ LLOQ in the Post-Treatment Period should have been completed as soon as possible.

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 each amplified by RT-PCR and then nested PCR using primers appropriate for subtype 1a or 1b sequences encoding NS3/4A protease, NS5A, or NS5B polymerase. The nested PCR amplification product was used as the template for DNA sequencing of the population of amplified molecules, performed under Good Laboratory Practice conditions in a 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 or became enriched as a result of treatment.

Noninferiority and Superiority Analyses

Historical SVR24 rates, as reported in the telaprevir US Prescribing Information[1] and Summary of Product Characteristics[2] for telaprevir plus pegylated interferon and ribavirin therapies in HCV genotype 1, treatment-naïve or treatment-experienced subjects with cirrhosis from the ADVANCE, ILLUMINATE, and REALIZE trials are presented the tables below. A fixed-effect meta-analysis was used to calculate the estimated SVR rate and 95% confidence interval (CI) in the treatment-naïve population (Table S1). A weighted average of the corresponding SVR rates among treatment-naïve and treatment-experienced (prior null responders, partial responders, and relapsers) subjects was calculated to reflect the population expected to enroll in TURQUOISE-II (Table S2).

For a regimen to be considered superior to the historical SVR rate for telaprevir plus pegIFN and RBV, the lower confidence bound (LCB) of the SVR rate for that regimen must exceed the upper confidence bound of the historical SVR rate for telaprevir plus pegylated interferon and ribavirin, presented in Table 2 (i.e., 54%). A noninferiority margin of 10.5% for comparisons to the historical SVR rate for telaprevir plus pegylated interferon and ribavirin was based on the telaprevir ILLUMINATE study,[3] which used the same noninferiority margin. Thus, to be considered noninferior to the historical SVR rate for telaprevir, the lower bound of the 95% CI for the SVR rate must be greater than the upper confidence bound of the SVR rate for the telaprevir-based therapy, minus 10.5% (i.e., 43%).

Table S1. SVR Rates for Telaprevir plus PegIFN and RBV in HCV Genotype 1 Treatment-Naïve Subjects

	ADVANCE	ILLUMINATE	Meta Analysis
Telaprevir Studies	**T12/PR n/N (%)**	**T12/PR n/N (%)**	**T12/PR % [95% CI]**
Treatment-naïve subjects with cirrhosis	15/21 (71)	31/61 (51)	56 [45, 67]

Table S2. Estimated SVR Rates for Telaprevir plus PegIFN and RBV in HCV Genotype 1 Cirrhotic Subjects

		REALIZE	
	Telaprevir-Treated Subjects with Cirrhosis n/N (%)	**Projected Enrollment in Study M13-099 (%)**	**Population-Based Weighted Average % [95% CI]**
Meta Analysis of ADVANCE and ILLUMINATE Studies (Table 1)			
Naïve Subjects	(56)	53	
REALIZE Study			
Prior relapsers	48/57 (84)	12	47 [41, 54]
Prior partial responders	11/32 (34)	12	
Prior null responders	7/50 (14)	23	

Sample Size

With a total sample size of about 380 subjects and assuming that 68% of the patients in each arm will achieve SVR_{12}, this study had greater than 90% power to demonstrate non-inferiority with a 2-sided 97.5% lower confidence bound greater than 43%, and 90% power to demonstrate superiority with a 2-sided 97.5% lower confidence bound greater than 54% (based on the normal approximation of a single binomial proportion in a one-sample test for superiority using EAST 5.4).[4-6] There was no adjustment for dropout because patients with no data at post-treatment week 12 (after imputing) were counted as failures for SVR_{12}.

For the comparison of SVR_{12} between treatment arms, a total sample size of approximately 380 subjects provided 80% power using Fisher's exact test with a 2-sided significance level of 0.05 to detect a difference of approximately 13% assuming underlying SVR_{12} rates of 68% and 81% in the 12- and 24-week arms, respectively. If the SVR_{12} rates were higher, then there was 80% power to detect a difference of approximately 10.5% with SVR_{12} rates of 80.5% and 91% in the 12- and 24-week arms, respectively.

Primary and Secondary Efficacy Endpoint Analyses

All efficacy analyses were performed on the ITT population.

The primary efficacy endpoint was the percentage of patients with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) within each treatment arm. The overall 2-sided significance level of 0.05 was split between the 2 arms using a Bonferroni correction of 0.025 for each arm. The percentage of patients achieving SVR_{12} within each treatment arm was calculated and a 2-sided 97.5% CI of the percentage was computed using the normal approximation to the binomial distribution.

A gatekeeping testing procedure (Figure S2) was used to control the Type I error rate at 0.05 and the primary endpoints within the 12-week arm were tested separately from the 24-week arm in the following order:

A1. SVR_{12}: noninferiority of the 12-week arm to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the lower confidence bound (LCB) of the 97.5% CI for the percentage of patients with SVR_{12} in the 12-week arm must have exceeded 43% to achieve noninferiority.

A2. SVR_{12}: superiority of the 12-week arm to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of patients with SVR_{12} in the 12-week arm must have exceeded 54% to achieve superiority.

B1. SVR_{12}: noninferiority of the 24-week arm to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of patients with SVR_{12} in the 24-week arm must have exceeded 43% to achieve noninferiority.

B2. SVR_{12}: superiority of the 24-week arm to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of patients with SVR_{12} in the 24-week arm must have exceeded 54% to achieve superiority.

Within the 12-week arm, only if success had been demonstrated for noninferiority of the SVR_{12} rate in the 12-week arm to the historical rate for telaprevir plus pegIFN and RBV therapy (A1) would the testing continue to superiority of the SVR_{12} rate in the 12-week arm to the historical rate for telaprevir plus pegIFN and RBV therapy (A2). Within the 24-week arm, only if success was demonstrated for noninferiority of the SVR_{12} rate in the 24-week arm to the historical rate for telaprevir plus pegIFN and RBV therapy (B1) would testing continue to superiority of the SVR_{12} rate in the 24-week arm to the historical rate for telaprevir plus pegIFN and RBV therapy (B2). Otherwise, statistical testing stopped. If success was achieved for all of the primary endpoints (A1, A2, B1, and B2), then the first secondary endpoint was tested; otherwise, statistical testing stopped.

The value of 54% used in the endpoints as the historical SVR rate for telaprevir plus pegIFN and RBV represents the upper confidence bound of the 2-sided 95% CI of the combined SVR rate. The value of 43% used for the noninferiority comparison represents the historical SVR rate (54%) adjusted for a noninferiority margin of 10.5%, after rounding.

The secondary efficacy endpoints were:

- the percentage of patients with SVR_{12} in the 24-week arm compared with the 12-week arm;
- the percentage of patients in each arm with on-treatment virologic failure during the Treatment Period (defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements > 1 log10 IU/mL above nadir) at any time point during treatment, or failure to suppress during treatment with at least 6 weeks of treatment);
- the percentage of patients in each arm with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among patients completing treatment and with HCV RNA < LLOQ at the end of treatment).

If success was demonstrated for all of the primary efficacy endpoints, then the multiple testing procedure continued to the first secondary efficacy endpoint to compare the percentage of patients with SVR_{12} following 12 or 24 weeks of treatment. To test the hypothesis that the percentages of patients who achieved SVR_{12} is different between the 12-week arm and the 24-week arm, the percentages were compared using a logistic regression model with treatment arm, baseline $\log_{10}$ HCV RNA level, HCV subgenotype (1a, non-1a), IL28B genotype (CC, non CC), and pegIFN/RBV treatment history (treatment-naïve or treatment-experienced) as predictors.

The percentages (with 2-sided 95% CIs using the normal approximation to the binomial distribution) of the patients with virologic failure during treatment and post-treatment relapse were calculated and summarized for each arm. These endpoints were not part of the multiple testing procedure, as no hypothesis was being tested.

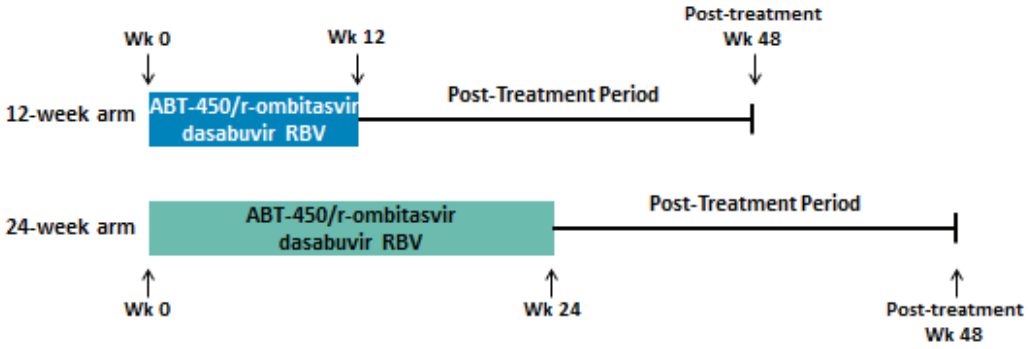
Subgroup analyses

The percentage (with 2-sided 95% CIs) of subjects with SVR_{12} for each treatment arm was presented for the following subgroups, if there were an adequate number of subjects within each subgroup. For each subgroup, the lower confidence bound of the 2-sided 95% CI was compared with 43%.

- treatment-naïve versus previous pegIFN/RBV treatment-experienced subjects
    - for treatment-experienced subjects, type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser);
- HCV genotype 1 subtype (1a, 1b, other);
- IL28B genotype (CC or non-CC), (CC, CT, or TT);
- baseline HCV RNA level (< 800,000 IU/mL or ≥ 800,000 IU/mL);
- baseline IP-10 (< 600 ng/L or ≥ 600 ng/L);
- baseline HOMA-IR (< 3 or ≥ 3 mU × mmol/L^2);
- sex (male versus female);
- age (< 55 versus ≥ 55 years), (< 65 versus ≥ 65 years);
- birth year (< 1945, 1945 to 1965, > 1965);
- race (black versus non-black);
- ethnicity (Hispanic versus no ethnicity);
- geographic region (North America, Europe) and country (as appropriate);
- BMI (< 30 or ≥ 30 kg/m^2);
- subjects with RBV dose modifications (yes/no);
- history of diabetes (yes/no);
- history of bleeding disorders (yes/no);
- history of depression or bipolar disorder (yes/no);
- former injection drug user (yes/no);
- baseline Child-Pugh score (5, 6, or > 6);
- baseline platelets (< 90 or ≥ 90 x 10^9/L);
- baseline albumin (< 35 or ≥ 35 g/L);
- baseline alpha fetoprotein (< 20 or ≥ 20 ng/mL)

A stepwise logistic regression was performed to assess the association of baseline subgroup factors with SVR_{12}. Continuous variables tested in the model were: age, body mass index, platelet count, serum albumin, serum alpha fetoprotein, and HCV RNA. Categorical variables were: treatment group (12 weeks vs 24 weeks); HCV subtype (1a, non-1a); IL28b genotype (cc, non-cc); previous treatment status (null responder, non-null responder); sex (female, male); race (black, non-black); region (Europe, North America); Child-Pugh score (5, >5); history of diabetes (yes, no); history of depression or bipolar disorder (yes, no); former injection drug user (yes, no); and ethnicity (Hispanic or Latino, non-Hispanic or -Latino). HOMA-IR and IP-10 were not included in the model, as many patients were missing these values. The significance level for entering predictors into and removing predictors from the model was 0.10.

Figure S1. Study design



ABT-450/r-ombitasvir 150 mg/100mg/25mg QD; dasabuvir 250 mg BID; RBV 1000 or 1200 mg daily dose divided BID, based on weight <75 or ≥75kg.

Figure S2. Decision rules in the multiple testing procedure.

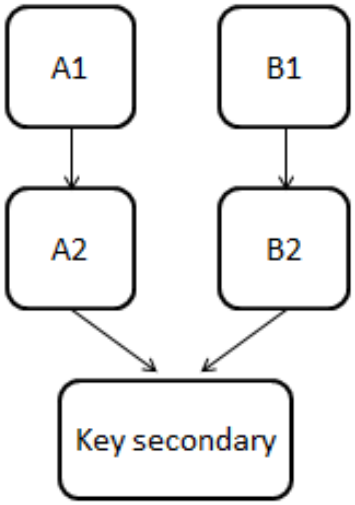
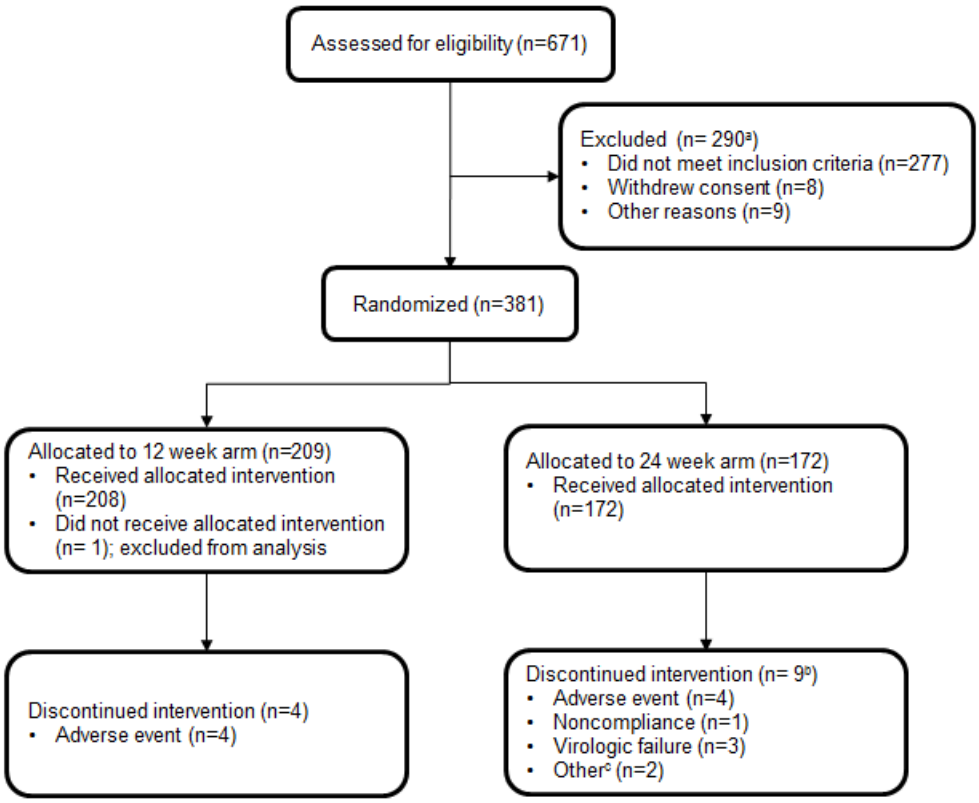


Figure S3: Patient disposition



[a] There could be more than one reason for screen failure.

[b] There could be more than one reason for discontinuation.

[c] Other reasons for discontinuation: 1 patient was incarcerated; 1 patient discontinued for personal issues unrelated to study drug. Both patients were considered treatment failures in the intent-to-treat analysis.

Table S3. SVR_{12} Rates According to Patient Subgroups

	12-week 3-DAA + RBV N=208	24-week 3-DAA + RBV N=172
Variable	Number with SVR_{12}/total number percent (95%CI)	
Sex		
Male	133/146 91.1 (86.5, 95.7)	116/121 95.9 (92.3, 99.4)
Female	58/62 93.5 (87.4, 99.7)	49/51 96.1 (90.8, 100.0)
Age		
< 55 years	53/58 91.4 (84.2, 98.6)	56/60 93.3 (87.0, 99.6)
≥ 55 years	138/150 92.0 (87.7, 96.3)	109/112 97.3 (94.3, 100.0)
Race		
Black	6/6 100.0 (N/A)	5/6 83.3 (N/A)
Non-black	185/202 91.6 (87.8, 95.4)	160/166 96.4 (93.5, 99.2)
Ethnicity		
Hispanic or Latino	21/25 84.0 (69.6, 98.4)	19/20 95.0 (85.4, 100.0)
Not Hispanic or Latino	170/183 92.9 (89.2, 96.6)	146/152 96.1 (93.0, 99.1)
Baseline body mass index		
< 30 kg/m^2	135/146 92.5 (88.2, 96.7)	122/126 96.8 (93.8, 99.9)
≥ 30 kg/m^2	56/62 90.3 (83.0, 97.7)	43/46 93.5 (86.3, 100.0)
History of diabetes		

Yes	25/29 86.2 (73.7, 98.8)	30/31 96.8 (90.6, 100.0)
No	166/179 92.7 (88.9, 96.5)	135/141 95.7 (92.4, 99.1)
History of depression or bipolar disorder		
Yes	48/51 94.1 (87.7, 100.0)	41/43 95.3 (89.1, 100.0)
No	143/157 91.1 (86.6, 95.5)	124/129 96.1 (92.8, 99.5)
Baseline Child-Pugh score		
5	158/170 92.9 (89.1, 96.8)	136/140 97.1 (94.4, 99.9)
6	33/38 86.8 (76.1, 97.6)	24/27 88.9 (77.0, 100.0)
>6	0	5/5 100.0 (N/A)
Baseline platelet count		
$<90x10^9$/L	25/30 83.3 (70.0, 96.7)	25/26 96.2 (88.8, 100.0)
$\geq 90x10^9$/L	166/178 93.3 (89.6, 96.9)	140/146 95.9 (92.7, 99.1)
Baseline albumin		
< 35 g/L	21/25 84.0 (69.6, 98.4)	16/18 88.9 (74.4, 100.0)
≥ 35 g/L	170/183 92.9 (89.2, 96.6)	149/154 96.8 (94.0, 99.6)
Baseline alpha fetoprotein		
< 20 ng/mL	145/152 95.4 (92.1, 98.7)	117/121 96.7 (93.5, 99.9)
≥ 20 ng/mL	46/56 82.1 (72.1, 92.2)	48/51 94.1 (87.7, 100.0)
Baseline HCV RNA		

< 800,000 IU/mL	31/34 91.2 (81.6, 100.0)	17/19 89.5 (75.7, 100.0)
≥ 800,000 IU/mL	160/174 92.0 (87.9, 96.0)	148/153 96.7 (93.9, 99.5)
HCV subtype		
Genotype 1a	124/140 88.6 (83.3, 93.8)	114/121 94.2 (90.1, 98.4)
Genotype 1b	67/ 68 98.5 (95.7, 100.0)	51/51 100.0 (100.0, 100.0)
IL28 genotype		
CC	33/35 94.3 (86.6, 100.0)	33/34 97.1 (91.4, 100.0)
non-CC	158/173 91.3 (87.1, 95.5)	132/138 95.7 (92.2, 99.1)
Treatment history		
Naïve	81/86 94.2 (89.2, 99.1)	70/74 94.6 (89.4, 99.7)
Experienced	110/122 90.2 (84.9, 95.4)	95/98 96.9 (93.5, 100.0)
Prior null responder	65/75 86.7 (79.0, 94.4)	59/62 95.2 (89.8, 100.0)
Prior partial responder	17/18 94.4 (83.9, 100.0)	13/13 100.0 (100.0, 100.0)
Relapser	28/29 96.6 (89.9, 100.0)	23/23 100.0 (100.0, 100.0)
Ribavirin dose modification		
Yes	18/18 100.0 (100.0, 100.0)	25/25 100.0 (100.0, 100.0)
No	173/190 91.1 (87.0, 95.1)	140/147 95.2 (91.8, 98.7)

Table S4. Outcomes for Patients Without SVR_{12}.

Reason	12 week 3-DAA + RBV N=208	24 week 3-DAA + RBV N=172
On-treatment virologic failure*	1/208 (0.5)	3/172 (1.7)
Relapse†	12/203 (5.9)	1/164 (0.6)
Other‡	4/208 (1.9)	3/172 (1.7)

* Confirmed virologic rebound or failure to suppress with at least 6 weeks of treatment.

† Confirmed HCV RNA ≥ 25 IU/mL post-treatment through SVR_{12} out of the patients completing treatment with HCV RNA < 25 IU/mL at end of treatment and with post treatment HCV RNA data.

‡ Patients not achieving SVR_{12} without on-treatment virologic failure or relapse (e.g., early discontinuation or loss to follow-up).

Table S5. List of Patients who Discontinued Due to Adverse Events

Patient sex, age	Adverse Event	Serious	Relationship to study treatment[a]
12-week arm			
Female, 25	Hepatitis acute	Yes	Reasonable possibility
Female, 64	Mental status change	No	Reasonable possibility
Female, 56	Extradural hematoma	Yes	No reasonable possibility
Female, 64	Nausea	Yes	Reasonable possibility
	Vomiting	Yes	Reasonable possibility
	Lactic acidosis	Yes	Reasonable possibility
24-week arm			
Female, 67	Anemia	Yes	Reasonable possibility
Female, 61	Chronic obstructive pulmonary disease	Yes	Reasonable possibility
Male, 51	Mood altered	No	Reasonable possibility
	Suicidal ideation	No	Reasonable possibility
Female, 62	Dysphagia	No	Reasonable possibility
	Asthenia	No	Reasonable possibility
	Retching	No	Reasonable possibility
	Tremor	No	Reasonable possibility
	Dizziness	No	Reasonable possibility
	Dehydration	No	Reasonable possibility

[a] Investigator's opinion of relationship to direct acting antiviral treatment

Table S6. List of Patients with Treatment Emergent Serious Adverse Events During the Treatment Period

Patient sex, age	Serious Adverse Event	Patient discontinued
12-week arm		
Male, 63	Atrial fibrillation	No
Female, 25	Hepatitis acute[†]	Yes
Male, 57	Clavicle fracture	No
	Wound	
Female, 59	Pneumonia	No
Female, 58	Cholecystitis acute	No
Female, 50	Femoral neck fracture	No
Female, 58	Major depression	No
Male, 58	Anemia	No
Female, 56	Extradural hematoma	Yes
Female, 64	Edema peripheral	Yes
	Nausea[†]	
	Vomiting[†]	
	Lactic acidosis[†]	
	Multi-organ failure	
	Rhabdomyolysis	
	Enterococcal bacteremia	
	Escherichia sepsis	
Male, 60	Hepatocellular carcinoma	No
Male, 63	Pharyngitis	No
	Candidiasis	
	Upper respiratory tract infection	
Male, 57	Toxicity to various agents	No
24-week arm		
Female, 67	Anemia[†]	Yes
Male, 65	Hepatocellular carcinoma	No

Female, 61	Chronic obstructive pulmonary disease[†] Intercranial aneurysm	Yes
Male, 60	Osteoarthritis	No
Male, 53	Cellulitis[†]	No
Male, 35	Blood glucose increased	No
Female, 70	Haematemesis Malaena Oesophageal varices haemorrhage	No
Male, 50	Fall Head injury	No

[†]Reasonable possibility of being related to direct acting antiviral treatment, in the opinion of the investigator.

Table S7. Treatment-Emergent Adverse Events Occurring in >5% of Patients in Either Arm During the Treatment Period

Event, n (%)	12 week N=208	24 week N=172	*P*-value
Fatigue	68 (32.7)	80 (46.5)	0.008
Headache	58 (27.9)	53 (30.8)	
Nausea	37 (17.8)	35 (20.3)	
Pruritus	38 (18.3)	33 (19.2)	
Insomnia	32 (15.4)	31 (18.0)	
Diarrhea	30 (14.4)	29 (16.9)	
Asthenia	29 (13.9)	22 (12.8)	
Rash	23 (11.1)	25 (14.5)	
Cough	24 (11.5)	19 (11.0)	
Irritability	15 (7.2)	21 (12.2)	
Anemia	16 (7.7)	18 (10.5)	
Dyspnea	12 (5.8)	21 (12.2)	0.029
Anxiety	15 (7.2)	14 (8.1)	
Dry skin	18 (8.7)	11 (6.4)	
Dizziness	18 (8.7)	10 (5.8)	
Muscle spasms	14 (6.7)	14 (8.1)	
Abdominal pain upper	11 (5.3)	16 (9.3)	
Decreased appetite	12 (5.8)	14 (8.1)	
Nasopharyngitis	13 (6.3)	13 (7.6)	
Arthralgia	10 (4.8)	14 (8.1)	
Dyspnea exertional	13 (6.3)	11 (6.4)	
Edema peripheral	13 (6.3)	10 (5.8)	
Pruritus generalized	10 (4.8)	12 (7.0)	
Blood bilirubin increased	12 (5.8)	9 (5.2)	
Vomiting	7 (3.4)	14 (8.1)	
Depression	8 (3.8)	12 (7.0)	
Upper respiratory tract infection	5 (2.4)	13 (7.6)	0.027

Back pain	4 (1.9)	13 (7.6)	0.011
Gastroesophageal reflux disease	7 (3.4)	10 (5.8)	
Hyperbilirubinemia	15 (7.2)	2 (1.2)	0.005
Memory impairment	5 (2.4)	12 (7.0)	0.044
Abdominal distension	6 (2.9)	9 (5.2)	

Comparisons between groups were made using Fisher's exact test. Only *P*-values <0.05 are shown.

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