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CLINICAL—LIVER

ABT-450, Ritonavir, Ombitasvir, and Dasabuvir Achieves 97% and 100% Sustained Virologic Response With or Without Ribavirin in Treatment-Experienced Patients With HCV Genotype 1b Infection

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BACKGROUND & AIMS: The interferon-free regimen of ABT-450 (a protease inhibitor), ritonavir, ombitasvir (an NS5A inhibitor), dasabuvir (a non-nucleoside polymerase inhibitor), and ribavirin has shown efficacy in patients with hepatitis C virus (HCV) genotype 1b infection—the most prevalent subgenotype worldwide. We evaluated whether ribavirin is necessary for ABT-450, ritonavir, ombitasvir, and dasabuvir to produce high rates of sustained virologic response (SVR) in these patients. **METHODS:** We performed a multicenter, open-label, phase 3 trial of 179 patients with HCV genotype 1b infection, without cirrhosis, previously treated with peginterferon and ribavirin. Patients were assigned randomly (1:1) to groups given ABT-450, ritonavir, ombitasvir, and dasabuvir, with ribavirin (group 1) or without (group 2) for 12 weeks. The primary end point was SVR 12 weeks after treatment (SVR12). We assessed the noninferiority of this regimen to the rate of response reported (64%) for a similar population treated with telaprevir, peginterferon, and ribavirin. **RESULTS:** Groups 1 and 2 each had high rates of SVR12, which were noninferior to the reported rate of response to the combination of telaprevir, peginterferon, and ribavirin (group 1: 96.6%; 95% confidence interval, 92.8%–100%; and group 2: 100%; 95% confidence interval, 95.9%–100%). The rate of response in group 2 was noninferior to that of group 1. No virologic failure occurred during the study. Two patients (1.1%) discontinued the study owing to adverse events, both in group 1. The most common adverse events in groups 1 and 2 were fatigue (31.9% vs 15.8%) and headache (24.2% vs 23.2%), respectively. Decreases in hemoglobin level to less than the lower limit of normal were more frequent in group 1 (42.0% vs 5.5% in group 2; $P < .001$), although only 2 patients had hemoglobin levels less than 10 g/dL. **CONCLUSIONS:** The interferon-free regimen of ABT-450, ritonavir, ombitasvir, and dasabuvir, with or without ribavirin, produces a high rate of SVR12 in treatment-experienced patients with HCV genotype 1b infection. Both regimens are well tolerated, as shown by the low rate of discontinuations and generally mild adverse events. ClinicalTrials.gov number: NCT01674725

Keywords: PEARL-II; Ribavirin-Free; IFN; Interferon-Free Therapy.

Untreated chronic hepatitis C virus (HCV) infection is a leading cause of liver damage, cirrhosis, and hepatocellular carcinoma.[1] The prevalence of HCV infection is estimated to be 3% worldwide and results in approximately 350, 000 deaths annually.[2,3] Genotype 1 accounts for approximately 70% of all HCV infections and subgenotype 1b is most predominant in Europe and Eastern Asia. Approved direct-acting antiviral agents (DAAs), telaprevir, boceprevir, sofosbuvir, and simeprevir, given with peginterferon (pegIFN) and ribavirin (RBV), have reported sustained virologic response (SVR) rates of 67%–89% in HCV genotype 1–infected patients. Response rates with DAA regimens are generally lower in patients who have failed previous pegIFN-containing treatment regimens than in treatment-naive

Abbreviations used in this paper: **AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DAA, direct-acting antiviral agent; HCV, hepatitis C virus; pegIFN, peginterferon; RBV, ribavirin; RT-PCR, reverse-transcription polymerase chain reaction; SVR, sustained virologic response; SVR12, sustained virologic response 12 weeks after treatment; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.**

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patients, and are noticeably lower among prior null responders.[4–8] In addition, the toxicity of pegIFN and long duration of therapy (up to 48 weeks with some regimens) are a hardship for patients.[9] Notably, pegIFN-based treatment regimens have well-documented adverse event (AE) profiles including influenza-like symptoms and depression, which have led to unfavorable discontinuation rates in clinical trials,[6,9–12] and RBV also has associated side effects including teratogenicity, hemolytic anemia, and rash.[13,14]

All-oral and interferon-free HCV treatment regimens with DAAs provide wider treatment access to patients in need with chronic liver disease. ABT-450 is an NS3/4A protease inhibitor with in vitro nanomolar antiviral activity and is co-dosed with the CYP3A4 inhibitor, ritonavir, which significantly increases peak and trough drug concentrations, enabling once-daily dosing.[15] The multitargeted, all-oral combination of the 3 DAAs of ABT-450/ritonavir, ombitasvir (formerly ABT-267), an HCV NS5A inhibitor with pangenotypic picomolar antiviral activity,[16] and dasabuvir (formerly ABT-333), an HCV NS5B RNA non-nucleoside polymerase inhibitor, with RBV was shown in a phase 2b trial to achieve high rates of SVR 12 weeks post-treatment (SVR12) in treatment-naive and treatment-experienced genotype 1–infected patients. With this regimen, a 93% SVR12 rate was achieved in genotype 1–infected noncirrhotic patients with prior null response to pegIFN/RBV, and a 100% SVR12 rate was achieved in the genotype 1b patient subset.[17] These high response rates in prior null responders, considered difficult to cure, are promising and require confirmation in a large phase 3 trial. Although ABT-450/ritonavir/ombitasvir and dasabuvir with RBV may achieve high SVR12 rates, determining the benefit gained by including RBV in the regimen has not been assessed in these patients. This phase 3 study (PEARL-II) evaluated the efficacy and safety of 12 weeks of treatment with coformulated ABT-450/ritonavir/ombitasvir and dasabuvir with or without RBV exclusively in noncirrhotic pegIFN/RBV treatment-experienced HCV genotype 1b–infected patients.

Materials and Methods

Patients

Adults were age 18–70 years at the time of screening from 43 sites in Austria, Belgium, Italy, The Netherlands, Portugal, Puerto Rico, Sweden, Switzerland, Turkey, and the United States. Patients were required to have documentation that they previously failed treatment with pegIFN/RBV. Eligible patients were required to be noncirrhotic with chronic HCV genotype 1b infection for at least 6 months with an HCV-RNA level greater than 10, 000 IU/mL at screening. Patients were excluded if they had evidence of co-infection with any HCV genotype other than 1b or tested positive for hepatitis B surface antigen or anti–human immunodeficiency virus antibody at screening. Detailed eligibility criteria are provided in the Supplementary Appendix.

Study Design

Patients were stratified by type of previous nonresponse to pegIFN/RBV treatment (null responders, partial responders, and relapsers) and randomized 1:1 to receive the 12-week regimen of coformulated ABT-450/ritonavir/ombitasvir (150/100/25 mg once daily) and dasabuvir (250 mg twice daily) with either weight-based RBV dosed twice daily (1000 mg daily if body weight $<$ 75 kg, 1200 mg daily if body weight was $\geq$ 75 kg) for group 1 or without RBV for group 2 (Supplementary Figure 1). After 12 weeks of treatment, patients were followed up for an 48 additional weeks. Additional details on study design are in the Supplementary Appendix.

The study was conducted in accordance with the International Conference of Harmonisation guidelines, applicable regulations, and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. All patients provided written informed consent. All authors had access to relevant data, and critically reviewed, revised, and approved the manuscript.

Safety Assessments

Adverse event assessments were reported from the time of study drug administration until 30 days after the last dose and were judged as mild, moderate, or severe; clinical laboratory testing was performed at each study visit. Serious AEs were recorded throughout the study.

Efficacy End Points

Plasma samples were collected at screening and at each study visit and HCV-RNA levels were determined using the Roche COBAS TaqMan real-time reverse-transcription polymerase chain reaction assay v2.0 (Roche Molecular Diagnostics, Pleasanton, CA) at a central laboratory. A fixed-sequence testing procedure was used to control type I error at 0.05. The primary efficacy end point was noninferiority of the SVR12 rates (assessed by HCV-RNA level $<$ 25 IU/mL) in group 2 and group 1 to the historical SVR12 rate for telaprevir plus pegIFN/RBV in HCV genotype 1b–infected patients who were relapsers, partial responders, or null responders to previous pegIFN/RBV treatment,[4] adjusted for noncirrhotic patients in this study. Group 1 and group 2 noninferiority could be claimed if the SVR12 lower limit of the 95% confidence interval (CI) was greater than the upper limit of the CI for the historical rate minus a 10.5% noninferiority margin (64%). Further details of historical noninferiority calculations are provided in the Supplementary Appendix. Secondary efficacy end points in the fixed sequence included the following: (1) comparison of the percentage of patients with a decrease in hemoglobin level to less than the lower limit of normal at the end of treatment; (2) superiority of group 1 and group 2 to the historical rate for telaprevir plus pegIFN/RBV (75%); and (3) noninferiority of group 2 to group 1 using a 10.5% noninferiority margin for the SVR12 difference. The percentage of patients with on-treatment virologic failure and post-treatment relapse also was assessed.

Virologic Failure Criteria

Virologic failure leading to discontinuation of study drug was determined if the following criteria occurred: confirmed increase from nadir in HCV-RNA level (defined as 2 consecutive HCV-RNA measurements greater than 1 $\log_{10}$ IU/mL greater than nadir) at any point during treatment; failure to achieve HCV-RNA level less than 25 IU/mL by week 6; and confirmed HCV-RNA level of 25 IU/mL or greater in 2 consecutive measurements at any point during treatment after HCV-RNA level

was less than 25 IU/mL. Post-treatment relapse was confirmed in patients with HCV-RNA level less than 25 IU/mL at the end of treatment and subsequent HCV-RNA level of 25 IU/mL or greater in 2 consecutive measurements.

Statistical Analyses

Efficacy analyses were performed using the intent-to-treat population, defined as all randomized HCV genotype 1b–infected patients who received at least one dose of coformulated ABT-450/ritonavir/ombitasvir. The safety population included all patients who received at least one dose of study drug. A population of 90 patients per treatment arm was calculated to provide greater than 90% power to achieve noninferiority of the active regimen to the historical threshold (64%).

SAS software (SAS Institute, Inc, Cary, NC) for the UNIX operating system was used for all analyses. All statistical tests and all confidence intervals were 2-sided with a significance level of .05.

Results

Baseline Patient Demographics and Characteristics

Patient screening began on August 14, 2012, and the final SVR12 data were collected on January 16, 2014. Of 324 patients screened, 187 were randomized and 186 received study drug (91 in group 1, 95 in group 2) (Supplementary Consort Flow Chart). Null responders, partial responders, and relapsers to previous pegIFN/RBV treatment comprised 34.9%, 28.5%, and 36.6% of the study population, respectively, evenly stratified between treatment arms (Table 1). Reasons for screen failures are provided in the Supplementary Appendix. Seven randomized patients, 3 in group 1 and 4 in group 2, were not included in the intent-to-treat efficacy population. Of these, 6 patients were enrolled before a protocol amendment and received noncoformulated ABT-450/ritonavir/ombitasvir, 3 of whom were genotype 1a; a seventh patient's HCV subgenotype was not determined.

Table 1. Baseline Demographics and Characteristics, n (%)

Parameter	Group 1 3D + RBV (N = 91)	Group 2 3D (N = 95)
Sex, male	45 (49.5)	57 (60.0)
Race		
White	84 (92.3)	86 (90.5)
Black	3 (3.3)	6 (6.3)
Ethnicity, Hispanic/Latino	4 (4.4)	2 (2.1)
Geographic region		
North America	14 (15.4)	19 (20.0)
Europe	77 (84.6)	76 (80.0)
Mean age, *y* (±SD)	54.2 ± 10.9	54.2 ± 10.5
Mean BMI, kg/m^2 (±SD)	26.2 ± 4.1	27.5 ± 4.3
IL28B genotype		
CC	10 (11.0)	7 (7.4)
Non-CC	81 (89.0)	88 (92.6)
Mean HCV-RNA level, log_{10} *IU/mL* (±SD)	6.56 ± 0.56	6.48 ± 0.53
Previous pegIFN/RBV nonresponse		
Null responder	32 (35.2)	33 (34.7)
Partial responder	26 (28.6)	27 (28.4)
Relapser	33 (36.3)	35 (36.8)
Baseline fibrosis stage		
F0–F1	64 (70.3)	61 (64.2)
F2	13 (14.3)	21 (22.1)
F3	14 (15.4)	13 (13.7)

NOTE. Fibrosis scoring information is provided in the Supplementary Appendix.
BMI, body mass index; IL, interleukin; 3D, 3 direct-acting antivirals.

Efficacy

After 12 weeks of treatment, 96.6% (85 of 88; 95% CI, 92.8–100) of group 1 and 100% (91 of 91; 95% CI, 95.9–100) of group 2 patients achieved SVR12 using the intent-to-treat population for both groups (Figure 1; Table 2, Supplementary Figure 2). For the primary end point, SVR12 rates in both treatment groups were noninferior to the historical SVR rate for telaprevir plus pegIFN/RBV in comparable treatment-experienced patients. Both treatment groups also were superior to the historical rate. Noninferiority of group 2 to group 1 was shown because the treatment difference in SVR12 rates was 3.4% (95% CI, -0.4 to 7.2).

No patients from either treatment group experienced on-treatment virologic failure or post-treatment relapse. Of the 3 patients in group 1 who did not achieve SVR12, there were 2 (2.3%) patients who discontinued study drug because of AEs, and 1 patient was lost to follow-up evaluation after SVR4 (Table 3).

Sustained virologic responses in both groups were not influenced by previous nonresponse, age, race, or interleukin 28B genotype. Among group 1 null responders, partial responders, and relapsers to previous pegIFN/RBV treatment, SVR12 rates were 93.5%, 96.0%, and 100%, respectively. Group 1 rates were similarly high regardless of interleukin 28B genotype (CC, 100%; CT, 96.4%; and TT, 95.5%), or sex (male, 95.3%; female, 97.8%). Group 2 SVR12 rates were 100% in all subgroups.

Finally, the 7 patients excluded from the efficacy subset because they received noncoformulated study drug, confirmed genotype 1a, or undetermined genotype, all completed treatment and achieved SVR12.

Safety

Treatment-emergent AEs (TEAE) were experienced by 79.1% of patients in group 1 and by 77.9% of patients in group 2. Most TEAEs were mild, with the most commonly reported events in group 1 and group 2 being fatigue (31.9% vs 15.8%; $P = .015$), headache (24.2% vs 23.2%; $P =$ NS), and nausea (20.9% vs 6.3%; $P = .005$), respectively (Table 3). Patients in group 1 also experienced statistically significantly more events of insomnia, anemia, rash, and increased blood bilirubin levels, all known to be associated with RBV use; no patient discontinued study drug because of these events.

Table 2. Intent-to-Treat Virologic Response

Parameter	Group 1 3D + RBV, n/N (%)	Group 2 3D, n/N (%)	Treatment difference (95% CI)
SVR12	85/88 (96.6)	91/91 (100)	3.4 (−0.4 to 7.2)
Previous nonresponse			
Null responder	29/31 (93.5)	32/32 (100)	6.5 (−2.2 to 15.1)
Nonresponder/partial responder	24/25 (96.0)	26/26 (100)	4.0 (−3.7 to 11.7)
Relapser	32/32 (100)	33/33 (100)	0 (N/A)
Sex			
Male	41/43 (95.3)	54/54 (100)	4.7 (−1.6 to 10.9)
Female	44/45 (97.8)	37/37 (100)	2.2 (−2.1 to 6.5)
Race			
Black	3/3 (100)	5/5 (100)	0 (N/A)
Non-black	82/85 (96.5)	86/86 (100)	3.5 (−0.4 to 7.5)
IL28B genotype			
CC	10/10 (100)	7/7 (100)	0 (N/A)
CT	54/56 (96.4)	64/64 (100)	3.6 (−1.3 to 8.4)
TT	21/22 (95.5)	20/20 (100)	4.5 (−4.2 to 13.2)

NOTE. The intent-to-treat genotype 1b efficacy population includes all patients with subgenotype 1b infection who were assigned to and treated with ABT-450/ritonavir/ombitasvir co-formulated drug.
IL, interleukin; N/A, not applicable; 3D, three direct-acting antivirals.

Overall, 2 (1.1%) patients discontinued treatment because of AEs, both in group 1. One patient experienced 2 serious AEs of pancreatitis that were considered by the investigator not to be study drug–related. This patient had increased amylase levels on day 1 before receiving study drug; on day 11, the patient reported abdominal pain and was hospitalized on day 13, at which point study drugs were discontinued. The patient experienced another mild episode of pancreatitis on day 31 that resolved by day 36. This patient had an HCV-RNA level of 28 IU/mL on day 8. Resistance analysis performed on baseline and post-treatment samples showed no NS3 or NS5B resistance-associated variants present at baseline. The NS5A R30Q variant was present at baseline, and R30Q and Y93H were present at post-treatment week 12. Another patient reported anxiety, tachycardia, fever, and dyspnea on day 36 that led to study discontinuation; HCV-RNA level on day 32 before discontinuation was less than 15 IU/mL. This patient had no resistance-associated variants in NS3 or NS5A at baseline; NS5B variants C316N and S556G were present at baseline and post-treatment week 4. Excluding the event of pancreatitis, 3 other serious TEAEs (cellulitis, nephrolithiasis, and osteoarthritis) were reported; none were judged to be study drug–related or led to study drug discontinuation.

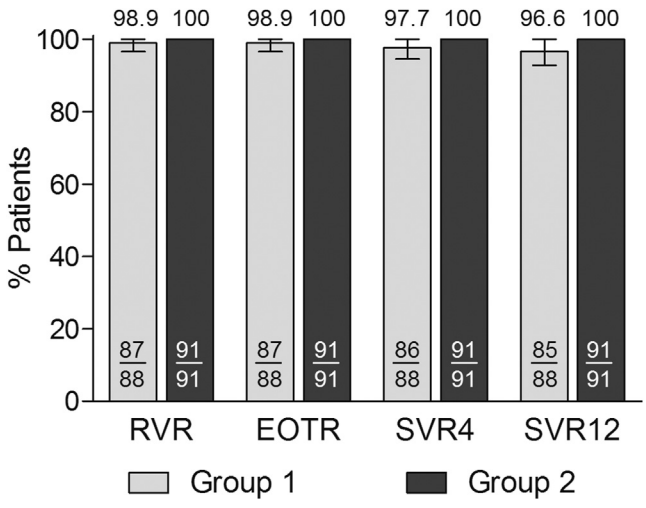

Figure 1. ITT genotype 1b efficacy subset treatment response over time. Percentage of patients achieving virologic response (±95% CIs) are presented for week 4 of treatment (RVR), end of treatment (EOTR), 4 weeks post-treatment (SVR4), and SVR12, as well as n/N within the bars graphs.

Hemoglobin levels less than the lower limit of normal at the end of treatment, a secondary end point, was experienced more often by patients in group 1 compared with patients in group 2 (42.0% vs 5.5%, respectively; $P < .001$), although clinically significant grade 2 hemoglobin level declines to less than 10 g/dL at the end of treatment occurred in only 2 (1.1%) patients, both in group 1. No patient required a blood transfusion or erythropoietin. Increases in total bilirubin level greater than 2 times the upper limit of normal (ULN) were reported in 15.4% of patients in group 1 and in 1.1% of patients in group 2 ($P < .001$), with 8.8% of patients in group 1 and 0% in group 2 reporting greater than 3 times the ULN. Mean levels of total bilirubin peaked at week 1 (predominantly indirect bilirubin) and were reduced at week 2 in both groups, although levels remained increased throughout the treatment period only in group 1 (Supplementary Figure 3). The mean total bilirubin level at week 1 was 1.6 mg/dL in group 1 and 0.9 mg/dL in group 2; by week 2, the mean levels were reduced to 1.2 and 0.7 mg/dL, respectively. Five (5.5%) patients in group 1 and 2 (2.1%) patients in group 2 reported hyperbilirubinemia; 3 (3.3%) patients in group 1 reported jaundice. One hyperbilirubinemia and 1 jaundice event were moderate in severity and the remaining events

Table 3. Patients Reporting TEAEs

Parameter	Group 1 3D + RBV, n (%) (N = 91)	Group 2 3D, n (%) (N = 95)	*P* value
Any TEAE	72 (79.1)	74 (77.9)	
Any severe TEAE	0 (0)	1 (1.1)	
Any serious TEAE	2 (2.2)	2 (2.1)	
TEAE leading to discontinuation	2 (2.2)	0 (0)	
Common TEAEs[a]			
Fatigue	29 (31.9)	15 (15.8)	.015
Headache	22 (24.2)	22 (23.2)	
Nausea	19 (20.9)	6 (6.3)	.005
Insomnia	13 (14.3)	3 (3.2)	.008
Pruritus	13 (14.3)	8 (8.4)	
Diarrhea	12 (13.2)	12 (12.6)	
Asthenia	11 (12.1)	7 (7.4)	
Anemia	10 (11.0)	0 (0)	<.001
Blood bilirubin level increased	8 (8.8)	0 (0)	.003
Rash	8 (8.8)	1 (1.1)	.017
Chemistry and hematologic values of interest during treatment			
Hemoglobin level < LLN at end of treatment[b]	37 (42.0)	5 (5.5)	<.001
Total bilirubin level > 3× ULN	8 (8.8)	0 (0)	.003
ALT level > 5× ULN	0 (0)	0 (0)	
AST level > 5× ULN	0 (0)	1 (1.1)	

LLN, lower limit of normal; ULN, upper limit of normal; 3D, three direct-acting antivirals.
[a]Investigator-reported TEAEs present in ≥ 10% of either treatment group or with a statistically significant difference between treatment groups.
[b]N = 88 and 91 for group 1 and group 2, respectively, using the intent-to-treat genotype 1b efficacy population.

were judged as mild; none led to study drug discontinuation. Ribavirin dose modification occurred in 5 patients, 3 owing to anemia, 1 owing to hyperbilirubinemia, and 1 was dose adjusted owing to a decrease in weight; all achieved SVR12.

The percentage of patients with postbaseline alanine aminotransferase (ALT) levels greater than 3 times the ULN was similarly low for both treatment groups. No patient experienced a postbaseline ALT level greater than 5 times the ULN. One patient in group 2 had an aspartate aminotransferase (AST) level greater than 5 times the ULN at a single study visit, all subsequent values were normal. Twelve weeks of treatment with these regimens normalized liver enzyme levels in almost all patients with high baseline liver enzyme levels: 96.9% (63 of 65) and 100% (66 of 66) of group 1 and group 2 patients, respectively normalized high baseline ATL levels after being treated; AST levels were normalized in 98.4% (60 of 61) and 91.8% (56 of 61) of group 1 and group 2 patients, respectively. Median changes from baseline in aminotransferase values at the final treatment visit were similar when comparing treatment groups (ALT, -35.0 vs -36.0 U/L; AST, -22.0 vs -21.0 U/L for group 1 and group 2, respectively).

Discussion

PEARL-II examined an all-oral, interferon-free regimen with or without RBV exclusively in pegIFN/RBV treatment-experienced, noncirrhotic patients with HCV genotype 1b infection. The intent-to-treat SVR12 rates of 96.6%–100% in patients receiving the 12-week regimen of ABT-450/ritonavir/ombitasvir and dasabuvir with or without RBV, respectively, were superior to the historical rate of telaprevir plus pegIFN/RBV. The SVR12 rates of this multitargeted regimen with RBV confirm results of the phase 2b AVIATOR study[17] in prior null responders, the most difficult to cure of pegIFN/RBV nonresponders, and further expands efficacy conclusions to patients who were partial responders and relapsers to pegIFN/RBV treatment. In addition, PEARL-II showed the noninferiority of the RBV-free regimen to the RBV-containing regimen, supporting the use of ABT-450/ritonavir/ombitasvir and dasabuvir without RBV for 12 weeks in the treatment of HCV genotype 1b–infected pegIFN/RBV-experienced patients without cirrhosis.

The TEAEs associated with either group in this 12-week regimen generally were mild and manageable. Overall, only 2 (1.1%) treated patients discontinued treatment because of AEs, and the 5 serious TEAEs reported in 4 patients were considered to be unrelated to study drug by the investigators. As expected, known RBV AEs (fatigue, nausea, insomnia, rash, anemia, and increased bilirubin level) were statistically more prevalent in group 1, although the frequency and severity appeared to be reduced compared with when RBV was combined with pegIFN.[7,18] Hemoglobin level decreases also were more frequent in group 1 although few (2.2%) reached clinical significance, and AEs leading to RBV dose reduction occurred in only 4 patients. Increased bilirubin levels in group 1 predominantly were caused by indirect bilirubinemia, consistent with the hemolysis associated with RBV and the known effect of ABT-450 on the bilirubin

transporter OATP1B1, although a lack of sustained bilirubin increases in group 2 suggest the predominant cause was RBV-related hemolysis. Liver enzyme level normalization was consistent with the high rate of virologic response.

The SVR12 rates reported here compare favorably with published reports of other interferon-free regimens using the NS5B RNA polymerase inhibitor sofosbuvir in combination with NS5A inhibitors (daclatasvir or ledipasvir), or with an NS3/4A protease inhibitor (simeprevir). Combinations of sofosbuvir plus daclatasvir with or without RBV have shown 95% or greater SVR12 in 41 treatment-experienced genotype 1 patients, of whom only 8 patients were genotype 1b.[19] Similar SVR12 rates have been reported in treatment-experienced genotype 1 patients with sofosbuvir plus ledipasvir with (21 of 21; 100%) or without (18 of 19; 95%) RBV, although only 6 genotype 1b patients were included.[20] In 13 genotype 1b–infected patients receiving the combination of simeprevir plus sofosbuvir with or without RBV, 100% SVR8 was reported.[21] A larger study of daclatasvir in combination with asunaprevir in pegIFN/RBV treatment-experienced genotype 1b–infected patients showed SVR12 rates of 80% (70 of 87) with patients not achieving an SVR primarily owing to a lack of efficacy and AEs.[22] Together with the results from PEARL-II, these data support a multitargeted approach to achieve SVR. Additionally, PEARL-II assessed efficacy exclusively in 179 genotype 1b-infected patients and was powered to analyze the contribution of RBV in treatment-experienced patients.

One of the strengths of the PEARL-II study includes its large sample size in genotype 1b–infected patients, the most prevalent subgenotype worldwide, including patients with previous null response and relapse to pegIFN/RBV treatment. Treatment-experienced genotype 1b–infected patients have not been studied extensively with currently approved or investigational IFN-free regimens, hence this large patient population represents a group with unmet need. Study limitations include the open-label study design; the exclusion of patients with cirrhosis, hepatitis B virus, or human immunodeficiency virus co-infection; and that these findings may be specific to genotype 1b–infected patients. However, the efficacy and safety of this regimen recently was described from phase 3 studies in treatment-naive patients infected with genotype 1a and 1b,[23] and in patients with cirrhosis.[24]

In conclusion, a 12-week regimen of ABT 450/ritonavir/ombitasvir and dasabuvir with or without RBV generally was well tolerated in pegIFN/RBV treatment-experienced, noncirrhotic, HCV genotype 1b–infected adults, as evidenced by the low rate of treatment discontinuation and serious AEs. In addition, the regimen without RBV was associated with fewer AEs of fatigue, nausea, insomnia, rash, and a lower rate of laboratory abnormalities including bilirubin level increase and hemoglobin level decrease. SVR rates of 96.6% and 100% were achieved, including 93.5% and 100% in the difficult-to-treat previous pegIFN/RBV null responders, with or without RBV, respectively. Therefore, ABT-450/ritonavir/ombitasvir and dasabuvir without RBV is sufficient to achieve optimal treatment of HCV genotype 1b infection in this population.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.04.045.

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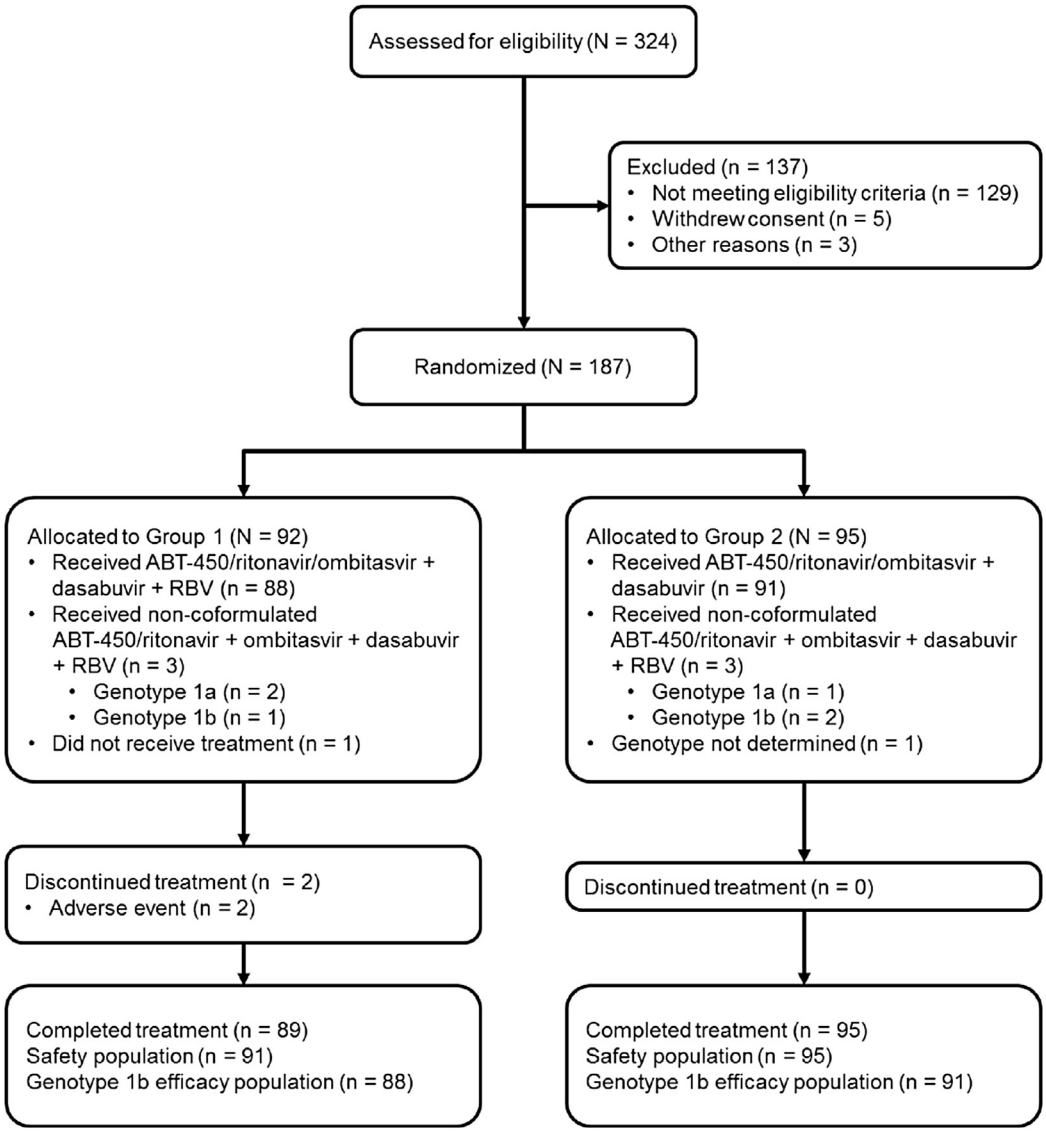

Supplementary Consort Flow Chart 1. Patient flow diagram.