Gastroenterology 2016;150:1590–1598

Efficacy of Direct-Acting Antiviral Combination for Patients With Hepatitis C Virus Genotype 1 Infection and Severe Renal Impairment or End-Stage Renal Disease

Paul J. Pockros,[1] K. Rajender Reddy,[2] Parvez S. Mantry,[3] Eric Cohen,[4] Michael Bennett,[5] Mark S. Sulkowski,[6] David E. Bernstein,[7] Daniel E. Cohen,[4] Nancy S. Shulman,[8] Deli Wang,[9] Amit Khatri,[10] Manal Abunimeh,[4] Thomas Podsadecki,[8] and Eric Lawitz[11]

[1]Division of Gastroenterology/Hepatology, Scripps Clinic and Scripps Translational Science Institute, La Jolla, California; [2]Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, Pennsylvania; [3]The Liver Institute at Methodist Dallas, Dallas, Texas; [4]Infectious Disease Development, AbbVie Inc, North Chicago, Illinois; [5]Medical Associates Research Group, San Diego, California; [6]Division of Infectious Diseases and Gastroenterology/Hepatology, Johns Hopkins University, Baltimore, Maryland; [7]Division of Gastroenterology, North Shore University Hospital, Manhasset, New York; [8]Global Pharmaceutical Development, AbbVie Inc, North Chicago, Illinois; [9]Statistics and Computer Sciences, AbbVie Inc, North Chicago, Illinois; [10]Clinical Pharmacokinetics, AbbVie Inc, North Chicago, Illinois; [11]Department of Gastroenterology, The Texas Liver Institute, University of Texas Health Science Center, San Antonio, Texas

CLINICAL LIVER

See Covering the Cover synopsis on page 1493.

BACKGROUND & AIMS: Although hepatitis C virus (HCV) infection is common in patients with end-stage renal disease, highly efficacious, well-tolerated, direct-acting antiviral regimens have not been extensively studied in this population. We investigated the safety and efficacy of ombitasvir co-formulated with paritaprevir and ritonavir, administered with dasabuvir (with or without ribavirin) in a prospective study of patients with stage 4 or 5 chronic kidney disease (CKD). **METHODS:** We performed a single-arm, multicenter study of treatment-naïve adults with HCV genotype 1 infection, without cirrhosis and with CKD stage 4 (estimated glomerular filtration rate, 15–30 mL/min/1.73 m^2) or stage 5 (estimated glomerular filtration rate, <15 mL/min/1.73 m^2 or requiring hemodialysis). Twenty patients were given ombitasvir co-formulated with paritaprevir and ritonavir, administered with dasabuvir for 12 weeks. Patients with HCV genotype 1a infections also received ribavirin (n = 13), whereas those with genotype 1b infection did not (n = 7). The primary end point was sustained virologic response (serum HCV RNA <25 IU/mL) 12 weeks after treatment ended (SVR12). We collected data on on-treatment adverse events (AEs), serious AEs, and laboratory abnormalities. **RESULTS:** All 20 patients completed 12 weeks of treatment. Eighteen of the 20 patients achieved SVR12 (90%; 95% confidence interval: 69.9–97.2). One patient death after the end of the treatment (unrelated to the treatment) and 1 relapse accounted for the 2 non-SVRs. Adverse events were primarily mild or moderate, and no patient discontinued treatment due to an AE. Four patients experienced serious AEs; all were considered unrelated to treatment. Ribavirin therapy was interrupted in 9 patients due to anemia; 4 received erythropoietin. No blood transfusions were performed. **CONCLUSIONS:** In a clinical trial, the combination of ombitasvir, paritaprevir, and ritonavir, administered with dasabuvir, led to an SVR12 in 90% of patients with HCV genotype 1 infection and stage 4 or 5 CKD. The regimen is well tolerated, though RBV use may require a reduction or interruption to manage anemia. ClinicalTrials.gov ID NCT02207088.

Keywords: NS5A Inhibitor; NS3/4A Protease Inhibitor; RUBY-I; Renal Disease.

Hepatitis C virus (HCV) infection is a global health problem with an estimated disease burden affecting 2.8% of the population.[1] In the United States, an estimated 2.7–3.5 million people have chronic HCV infections, and those who are current or former injection drug users, human immunodeficiency virus–positive, on hemodialysis, or from highly endemic countries, are known to be at increased risk.[2,3] HCV seroprevalence in the hemodialysis population has ranged from 7.8% to 44% in the United States and other developed countries.[4–7] In patients with chronic kidney disease (CKD), the risks for negative outcomes are significantly higher in HCV-infected patients than in those without infection, including progression to cirrhosis, hepatocellular carcinoma, liver-related mortality, and progression to end-stage renal disease (ESRD).[4,8–10] While HCV infection is associated with several glomerulopathies, longstanding hypertension and type 2 diabetes still account for most cases of ESRD and mortality in this population.[4,11] In

Abbreviations used in this paper: **AE, adverse event; CKD, chronic kidney disease; C_{trough}, steady-state trough concentration; DAA, direct-acting antiviral; DSV, dasabuvir; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GT, genotype; IFN, interferon; LLOQ, lower limit of quantification; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; SVR, sustained virologic response; SVR12, sustained virologic response at post-treatment week 12.**

Most current article

0016-5085

http://dx.doi.org/10.1053/j.gastro.2016.02.078

patients who have received a kidney transplant, HCV-associated liver disease increases the risk for graft rejection, proteinuria, infection, and diabetes[12]; therefore, eradication of HCV infection before transplantation can improve outcomes in these patients.

Historically, treating HCV infection in patients with CKD was challenging because of toxicities associated with the use of interferon (IFN). Reduced renal clearance of IFN increases the risk and severity of IFN-related adverse reactions, including flu-like symptoms, depression, and cytopenias. Low sustained virologic response (SVR) rates of 33%–37% and discontinuation rates of 17%–30% further limit IFN's applicability.[13,14] The toxicity of IFN in this population is aggravated by the concomitant use of renally excreted ribavirin (RBV), which is minimally eliminated by hemodialysis; thus, the combination of IFN and RBV is associated with substantial hematologic toxicity in a population already at risk for anemia.[15] Although RBV can be used with dosage modifications in patients with impaired renal function,[16,17] the majority of HCV-infected patients with ESRD have gone untreated.

Breakthroughs in our understanding of the HCV lifecycle and the ability to directly interfere with viral replication within hepatocytes have revolutionized treatment of HCV. The new generation of direct-acting antivirals (DAAs) offers shorter, IFN-free, well-tolerated, highly efficacious curative therapies. Rates of SVR for these new DAA combinations approach 95%–100% for HCV genotype (GT) 1[18,19]; however, data are limited in patients with CKD. Ombitasvir (OBV) is an HCV NS5A inhibitor that is co-formulated with paritaprevir (PTV), an NS3/4A protease inhibitor and the pharmacokinetic enhancer ritonavir (r), and is coadministered with dasabuvir (DSV), a non-nucleoside NS5B polymerase inhibitor, for treatment of GT1 HCV, the most common genotype. This regimen has shown high rates of SVR at post-treatment week 12 (SVR12) in patients with GT1 infection, synonymous with viral cure.[20] Phase 3 studies of this regimen were conducted in >2000 patients with HCV GT1 infection without ESRD, with and without compensated cirrhosis, and with or without prior pegylated IFN/RBV treatment experience.[21–25] When used according to the dosing recommendations in the US label, this regimen achieved SVR in 95.8% of patients with GT1a infection, and 99.7% of patients with GT1b infection.[26,27]

As OBV, PTV, DSV, and ritonavir are all hepatically metabolized with minimal renal clearance, the pharmacokinetics of these DAAs were evaluated in HCV seronegative persons with mild (creatinine clearance 60–89 mL/min), moderate (creatinine clearance 30–59 mL/min), and severe (creatinine clearance 15–29 mL/min) renal impairment. The plasma exposures observed supports use of this regimen in HCV-infected patients with renal impairment with no need for dose adjustments.[28] The RUBY-I study investigated the efficacy and safety of OBV/PTV/r plus DSV with or without RBV in treatment-naïve HCV GT1-infected patients with stage 4 or 5 CKD, including those on hemodialysis.

Methods

Patients and Study Design

Cohort 1 of this study enrolled noncirrhotic adults 18 years or older with stage 4 or 5 CKD and HCV GT1 infection (HCV RNA >1000 IU/mL at screening) who had never been treated for HCV infection. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation:

$$eGFR = 175 \times (Serum\ Creatinine)^{-1.154} \times Age^{-0.203} \times (0.742\ if\ female) \times (1.21\ if\ black\ race).$$

Stage 4 and 5 CKD was defined as an eGFR of 15–30 mL/min/1.73 m^2 and <15 mL/min/1.73 m^2, respectively; those on hemodialysis were considered to have stage 5 CKD or ESRD. Plasma samples collected at screening were assessed to determine HCV genotype using the Versant HCV Genotype Inno LiPA Assay, version 2.0 or higher (Siemens Healthcare, Berkeley, CA). Exclusion criteria included co-infection with hepatitis B, human immunodeficiency virus, or non-GT1 HCV, patients on peritoneal hemodialysis, history of solid organ transplant, and laboratory values for albumin <2.8 g/dL, hemoglobin <10 g/dL, platelet count <25,000 × 10^9/L, total bilirubin ≥3.0 mg/dL, or an international normalized ratio >2.3.

Cohort 1 of this study included patients without cirrhosis only. Patients were considered to be noncirrhotic as determined by liver biopsy within 24 months before or during screening (METAVIR score of ≤3, Ishak score of ≤4). In the absence of a biopsy, patients must have had a screening FibroTest score of ≤0.72 and an aspartate aminotransferase to platelet ratio index ≤2, or a screening transient elastography (eg, FibroScan) result of <12.5 kPa. Fibrosis stage was determined according to these tests and additional details are provided in the Supplementary Material (Supplementary Table 1).

The study consisted of a 12-week treatment period followed by a 24-week post-treatment period. Treatment regimens for patients with HCV GT1a and GT1b infection differed in accordance with the US prescribing information for OBV/PTV/r plus DSV.[29] Patients with GT1a infection received open-label OBV/PTV/r (25/150/100 mg once daily) plus DSV (250 mg twice daily) plus RBV (200 mg once daily) for 12 weeks; GT1b-infected patients received this regimen without RBV for 12 weeks. Study drug could be administered at any time without regard for timing of hemodialysis.

All patients signed an informed consent, and the study was conducted in accordance with the protocol, International Conference on Harmonization guidelines, and ethical principles that have their origin in the Declaration of Helsinki. All authors had access to relevant data and reviewed and approved the final manuscript.

Efficacy, Safety, Resistance, and Pharmacokinetic Assessments

Plasma samples were collected at screening and each study visit, and were processed by a central laboratory. Efficacy was assessed by achievement of an SVR12, defined as an HCV RNA below the level of quantification (LLOQ) using the Roche COBAS

TaqMan real-time reverse transcriptase polymerase chain reaction assay, version 2.0 (Roche Molecular Systems, Pleasanton, CA). For this assay, the lower limit of detection for HCV RNA is 15 IU/mL and the LLOQ is 25 IU/mL. The primary end point was the percentage of patients with SVR12. Secondary end points included the percentage of patients with on-treatment virologic breakthrough or post-treatment relapse. Breakthrough was defined as an HCV RNA greater than or equal to the LLOQ after an HCV RNA was lower than LLOQ during treatment or confirmed increase >1 $\log_{10}$ IU/mL above nadir in 2 consecutive HCV RNA measurements. Relapse was defined as a confirmed HCV RNA greater than or equal to the LLOQ between the end of treatment and post-treatment week 12 for those completing treatment with an HCV RNA lower than the LLOQ.

Adverse events (AEs) occurring from the start of study-drug administration until 30 days after the last dose were collected using the MedDRA System Organ Class and preferred term and were assessed by the investigator for relation to study drug and severity. Serious AEs were collected from the time of signed consent until 30 days after the last dose of study drug. Physical examination with measurement or vital signs and laboratory assessments were also conducted at each study visit.

A baseline plasma sample was collected before dosing on day 1 for all patients. Viral RNA isolated from these samples was analyzed by population sequencing (sensitivity threshold for variant detection 10%–15%) for variants at signature resistance-associated positions within the relevant targets, NS3, NS5A, or NS5B. In patients experiencing virologic failure, the closest sample in time taken after failure with an HCV RNA >1000 IU/mL was analyzed by population sequencing for identification of resistance-associated variants.

Pharmacokinetic samples were collected from patients during each study visit. Patients consenting to intensive pharmacokinetic sampling had samples drawn at the week 4 study visit at hour 0 (before study drug administration) and approximately 2, 4, 5, 6, 8, 12, and 24 hours post-DAA dose. Plasma concentrations for OBV, PTV, ritonavir, DSV, DSV principal metabolite, and RBV were summarized as steady-state trough levels (C_{trough}) based on binning of samples using time of sample collection after dosing, such that concentrations that fall in the interval of 10 to 14 hours and 22 to 26 hours after dosing were considered as C_{trough} for twice a day and every day dosing, respectively.

Ribavirin Management for Decreases in Hemoglobin

Patients receiving RBV who experienced a decline in serum hemoglobin >2 g/dL during any 4-week period, or had any hemoglobin value <10 g/dL, interrupted RBV dosing. If the hemoglobin level increased above the level that triggered the interruption, RBV could be resumed at the discretion of the investigator. Hematologic growth factors or blood transfusions were permitted at the discretion of the investigator.

Statistical Analyses

All efficacy and safety analyses were performed on the intent-to-treat population, defined as all patients receiving at least 1 dose of study drug. A prespecified modified intent-to-treat analysis was conducted, excluding patients who did not achieve SVR12 for reasons other than virologic failure. Two-sided 95% confidence intervals were calculated using the Wilson score method for binomial proportions. SAS, version 9.0, for the UNIX operating system (SAS Institute, Cary, NC) was used for all analyses.

Table 1. RUBY-I Baseline Demographics and Disease Characteristics

Variable	OBV/PTV/r + DSV ± RBV (n = 20)
Age, *y*, median (range)	60 (49–69)
Male, n (%)	17 (85)
Black race, n (%)	14 (70)
Hispanic or Latino ethnicity, n (%)	3 (15)
BMI, *kg/m²*, median (range)	30.5 (20.3–37.1)
HCV GT1a, n (%)	13 (65)
IL28B non-CC genotype, n (%)	14 (70)
Fibrosis stage, n (%)	
F0–F1	10 (50)
F2	6 (30)
F3	4 (20)
HCV RNA, *log₁₀ IU/mL*, median (range)	6.6 (5.5–7.6)
History of diabetes, n (%)	11 (55)
CKD stage, n (%)	
4 (eGFR 15–30 mL/min/1.73 m²)	6 (30)
5 (eGFR <15 mL/min/1.73 m², or requiring hemodialysis)	14 (70)
eGFR, *mL/min/1.73 m²*, median (range)	10.9 (5.4–29.9)
Creatinine, *mg/dL*, median (range)	6.2 (2.2–10.8)
Creatinine clearance, *mL/min*, median (range)	18.1 (8.9–63.1)
Hemoglobin, *g/dL*, median (range)	12.0 (9.5–16.6)
Total bilirubin, *mg/dL*, median (range)	0.4 (0.2–0.7)
Albumin, *g/dL*, median (range)	4.2 (3.0–4.6)
Platelet count, *×10⁹/L* median (range)	230 (90–432)
INR, median (range)	1.05 (0.90–1.60)

BMI, body mass index; IL28B, interleukin 28B; INR, international normalized ratio.

Results

Baseline Patient Demographics and Viral Resistance

Thirty-one patients were screened from September 23, 2014 through February 18, 2015 at 7 sites within the United States for cohort 1 of this study. Twenty treatment-naïve patients were enrolled including 13 with HCV GT1a infection who received OBV/PTV/r + DSV + RBV, and 7 with GT1b infection who received treatment without RBV (Supplementary Figure 1). The majority of patients were male, reported black race, and had stage 5 CKD with 14 patients on hemodialysis (Table 1). At baseline, median creatinine was 6.2 mg/dL, creatinine clearance was 18.1 mL/min, eGFR was 10.9 mL/min/1.73 m^2, and hemoglobin was 12.2 g/dL.

At baseline, variants known to convey resistance to some inhibitors of HCV NS3, NS5A, and NS5B (non-nucleoside) were present in the majority of patients. The NS3 variant

Table 2. On-Treatment and Post-Treatment Virologic Response, and Reasons for Nonresponse

Response	OBV/PTV/r + DSV ± RBV (n = 20)
HCV RNA <25 IU/mL	
During treatment	
At wk 4	19 (95)
At wk 12	20 (100)
After treatment	
At wk 4	18 (90)
At wk 12	18 (90)
Virologic breakthrough during treatment	0
Relapse[a]	1 (5)
Missing SVR12	1 (5)[b]

NOTE. Values are n (%).
[a]Virologic relapse was defined as a confirmed HCV RNA level of ≥25 IU/mL between the final visit and 12 wk after the last dose of study drugs among patients who had an HCV RNA level of <25 IU/mL at the final visit.
[b]Patient died on post-treatment day 14 for reasons unrelated to study drug.

Q80K/L was detected in 10/13 GT1a-infected patients, and NS5B S556G was detected in 1 patient. The Q80K variant confers an approximately 3-fold resistance to PTV, and S556G variant confers an approximately 30-fold resistance to DSV. No resistance-associated variants were detected in NS5A among GT1a-infected patients. In GT1b-infected patients, NS5A variants L28M, Q54N, or Q62R were each detected in 1 patient, and Q54H was detected in 3 patients; no resistance-associated variants were detected in NS3 or NS5B in GT1b-infected patients. The NS5A variants detected in GT1b-infected patients are not associated with resistance to OBV (L28M and Q54H) or have not previously been selected by OBV therapy (Q54N and Q62R).

Efficacy Outcomes

Plasma HCV RNA was suppressed less than the LLOQ in 15 of 20 (75%) patients by week 2, and in 19 of 20 (95%) patients by treatment week 4 (Table 2). All 20 patients completed 12 weeks of treatment and all were virologically suppressed at the end of treatment. The intent-to-treat SVR12 rate was 90% (18 of 20; 95% confidence interval: 69.9–97.2). For the 2 patients not achieving SVR12, 1 patient with HCV GT1a infection died 14 days after completing treatment of cardiac disease, considered by the investigator to be unrelated to study drug or RBV. The other patient who failed to achieve SVR12 had virologic relapse at post-treatment week 4. This patient, a 49-year-old black male on hemodialysis, had HCV GT1a infection and F3 fibrosis, an interleukin 28B CT genotype, and a body mass index of 36.8 kg/m^2. Of note, this patient had relatively low reported dose adherence for OBV/PTV/r (91.8%), and lower adherence for DSV (91.2%) than most of the other patients. By comparison, the mean pill count compliance for OBV/PTV/r was 98.7%, and 96.8% for DSV in the 19 other patients. In addition, RBV was interrupted on day 58 due to a hemoglobin decline to 9.8 g/dL (Figure 1*F*). No significant NS3 or NS5A variants were present at baseline, although resistance-associated variants D168V in NS3 and Q30R in NS5A were present at the time of virologic failure. Additional characteristics for the 2 patients not achieving SVR12 are provided in Supplementary Table 2.

The modified intent-to-treat SVR12 rate was 95% (18 of 19; 95% confidence interval: 75.4%– 99.1%). Examining patients with GT1a infection, the intent-to-treat SVR12 was achieved in 85% (11 of 13) and modified intent-to-treat SVR12 rate was 92% (11 of 12). No patients with GT1b infection failed treatment, thus, the SVR12 rate was 100% (7 of 7).

Safety Outcomes

Most patients experienced AEs, the majority of which were mild or moderate in severity (Table 3). No patient discontinued DAAs due to AE. The most common AEs were anemia (45%), fatigue (35%), diarrhea (25%), and nausea (25%). Nine treatment-emergent serious AEs were reported in 4 patients, although none were attributed to DAAs or RBV. Serious AEs are summarized in Supplementary Table 2. Post-baseline grade 3 abnormalities were rare, with 1 patient having a hemoglobin decline <8 g/dL, described here. No patients had any signs of hepatic decompensation.

One patient died 14 days after completing 12 weeks of therapy. This 60-year-old male on hemodialysis with a history of hypertension was hospitalized on post-treatment day 2 with hypertensive urgency after reporting nausea, emesis, and abdominal and flank pain. Pulmonary edema was identified and congestive heart failure (ejection fraction 15%) was diagnosed on the second day of hospital admission. On days 11 and 12 of hospitalization, the patient experienced lower gastrointestinal bleeding, became hemodynamically unstable, and expired due to cardiac arrest. The patient's hemoglobin level was stable (9–11 g/dL) during the final 6 weeks of treatment, and was 10 g/dL at the time of hospitalization, suggesting that RBV-induced anemia likely did not contribute to the cardiac event. Before his death, this patient's last post-treatment laboratory values included an international normalized ratio of 1.2, albumin of 3.7 g/L, and a total bilirubin of 0.7 mg/dL.

Anemia and Management of Hemoglobin Declines

Hemoglobin change (mean ± SD) was −1.38 ± 1.54 g/dL in patients receiving RBV, and −0.02 ± 0.90 among those receiving OBV/PTV/r + DSV alone. Anemia was the most common AE (n = 9), and was reported only in GT1a-infected patients receiving DAAs + RBV. Ribavirin was interrupted in all 9 of these patients and erythropoietin was administered to 4 patients, including 2 who had used erythropoietin before starting treatment; no patient received a blood transfusion. Interruption of RBV occurred as early as the first week of treatment in 2 patients (Figure 1*A* and *B*), and as late as day 74 (Figure 1*C*). Three patients resumed RBV dosing after improvement in

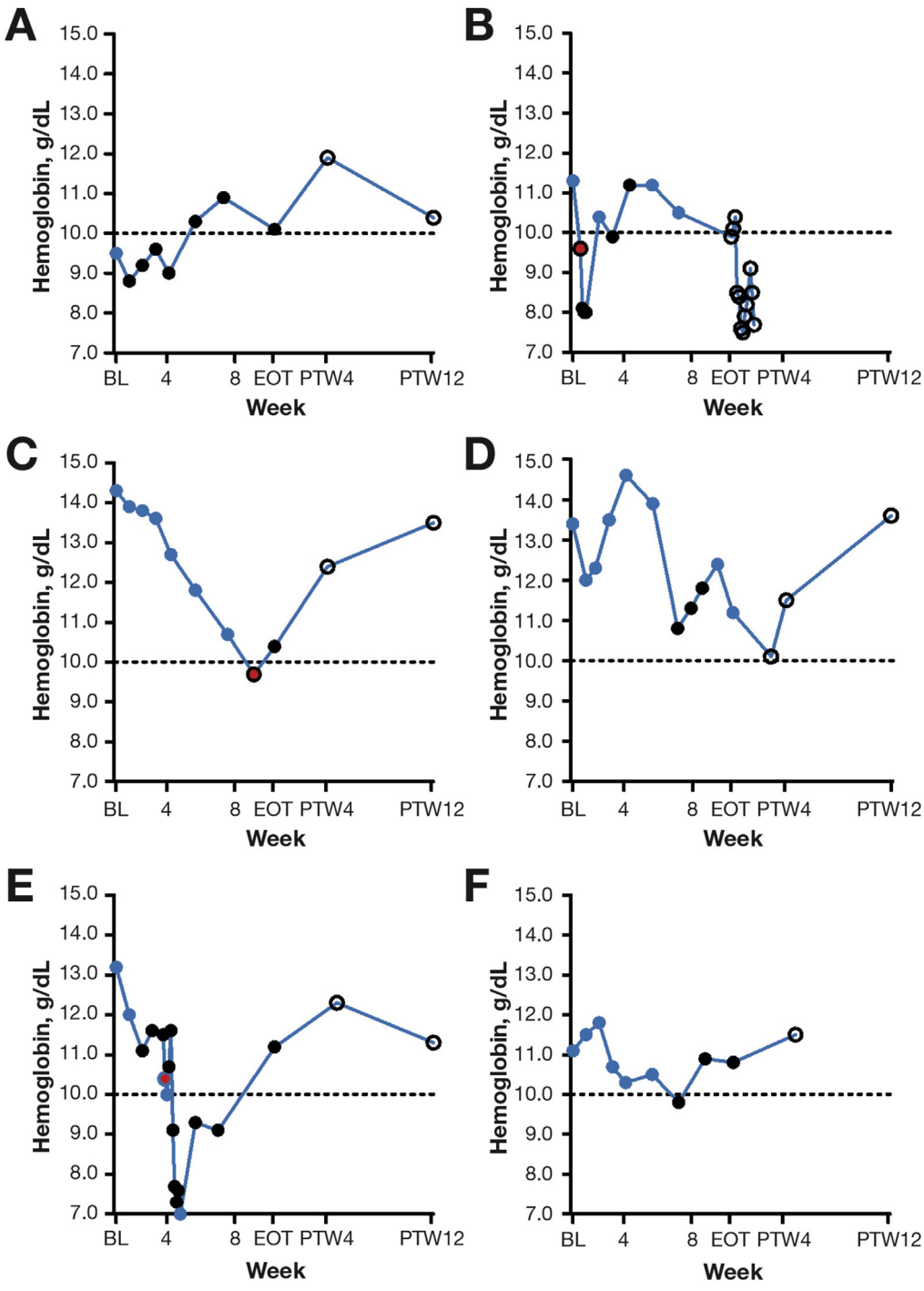

Figure 1. Hemoglobin levels for patients interrupting RBV. Nine patients interrupted RBV due to hemoglobin declines. Plotted are individual patient hemoglobin levels over time for 6 patients; plots for the remaining 3 patients are located in Supplementary Figure 2. Ribavirin was resumed in 3 patients (*B*, *D*, and *E*). *Blue-filled symbols* indicate RBV administration. *Black-filled symbols* indicate when RBV was interrupted. *Red-filled symbols* indicate administration of erythropoietin. *Open symbols* indicate hemoglobin levels during the post-treatment period. The *horizontal dotted line* demarcates 10 g/dL. BL, baseline; EOT, end of treatment; PTW, post-treatment week.

hemoglobin levels (Figure 1*B*, *D*, and *E*); the remaining 6 patients completed treatment without the resumption of RBV. In general, RBV interruption led to improvements in hemoglobin levels at subsequent on-treatment study visits. Among the 7 GT1b-infected patients who received OBV/PTV/r + DSV without RBV, 2 patients had hemoglobin measurements <10 g/dL, including one whose baseline value was <10 g/dL.

One patient experienced a grade 3 hemoglobin value (<8 g/dL), which was related to incorrect RBV dosing during a hospitalization for a spinal fracture and diskitis (Figure 1*E*). Ribavirin dosing had been interrupted during the hospitalization beginning on study day 17, but the patient received extra RBV doses on day 27 (400 mg total) and day 28 (600 mg total). Ribavirin was then interrupted again, and erythropoietin was administered beginning on day 28. The patient's hemoglobin level declined to 7.7 g/dL on day 32 and to a nadir value of 7.0 g/dL on day 35, but subsequently improved and was >10 g/dL by the end of treatment. The patient achieved SVR12.

Table 3. Treatment-Emergent Adverse Events and Laboratory Abnormalities

Variable	GT1a OBV/PTV/r + DSV + RBV (n = 13)	GT1b OBV/PTV/r + DSV (n = 7)
Any AE	13 (100)	6 (86)
Any AE assessed as being related to DAAs	8 (62)	2 (29)
Serious AE	3 (23)	1 (14)
AE leading to study drug discontinuation	0	0
Death	1 (8)	0
AEs occurring in ≥15% of patients		
Anemia	9 (69)	0
Fatigue	5 (38)	2 (29)
Diarrhea	4 (31)	1 (14)
Nausea	5 (38)	0
Headache	3 (23)	0
Peripheral edema	1 (8)	2 (29)
Hemoglobin		
Grade 2 (<10–8 g/dL)	7 (54)	2 (29)
Grade 3 (<8–6.5 g/dL)	1 (8)	0
Total bilirubin		
Grade 2 (>1.5–3 × ULN)	2 (15)	0
Grade 3 (>3–20 × ULN)	0	0
Alanine aminotransferase		
Grade 3 (>5–20 × ULN)	0	0
Aspartate aminotransferase		
Grade 3 (>5–20 × ULN)	0	0

NOTE. Values are n (%).
ULN, upper limit of normal.

Pharmacokinetic Results

The binned geometric mean trough plasma concentrations of PTV, ritonavir, OBV, and DSV in patients with stages 4 and 5 CKD were generally comparable with the values in HCV GT1-infected patients without ESRD enrolled in phase 3 studies of these DAAs (Figure 2). The C_{trough} geometric means for DSV principal metabolite and RBV were approximately 15%–38% lower and 27%–36% lower, respectively, compared with the range of values observed in phase 3 studies in patients without ESRD. Intensive pharmacokinetic data were available from 3 patients: 1 with stage 4 CKD, 1 with stage 5 ESRD obtained on a nonhemodialysis day, and 1 with stage 5 ESRD obtained on a hemodialysis day. Due to the limited sample size, these data are not summarized here. For the stage 5 CKD patient with pharmacokinetic data collected during hemodialysis, the arterial and venous concentrations of all DAAs were comparable (<17% change) before the start of hemodialysis, 1 hour after the start of hemodialysis, and at the end of hemodialysis. Although these data are limited, they suggest that hemodialysis does not extract these DAAs or ritonavir from the bloodstream.

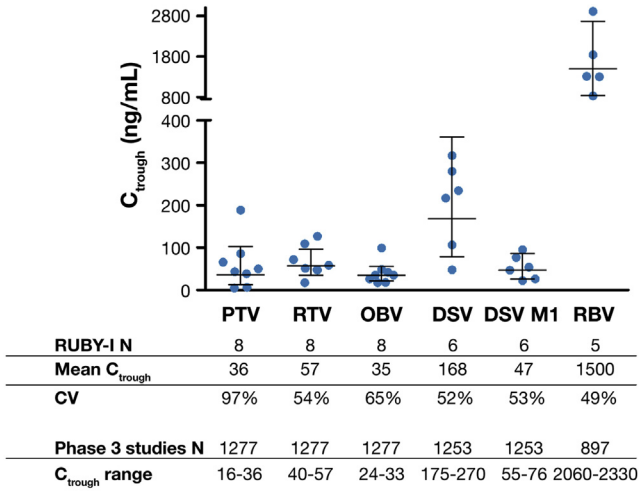

Figure 2. Mean plasma trough concentrations for study drugs. Individual patients' plasma drug trough concentrations are plotted using a binned time interval of >22–26 hours for PTV, RTV, and OBV, and an interval of >10–14 hours for DSV, DSV M1, and RBV. *Horizontal lines* and the *table* indicate the geometric mean in ng/mL; *whiskers* indicate 95% confidence intervals. DSV M1, dasabuvir principal metabolite; CV, coefficient of variation.

Discussion

Before the era of IFN-free treatment regimens, few HCV-infected patients with ESRD underwent HCV treatment due to the toxicity and poor tolerability of the available regimens. As such, these patients have not benefitted from HCV cure and have remained at risk for liver disease progression, including complications of cirrhosis, hepatocellular carcinoma, and death. New treatment paradigms have emerged with the use of DAAs, with new opportunities for cure in this difficult-to-treat population. In this study, 20 patients with HCV GT 1 infection and severe CKD or ESRD, including those

on hemodialysis, received 12 weeks of OBV/PTV/r + DSV with or without RBV. The SVR12 rate was 90% with 1 patient relapsing after treatment and 1 patient death during the post-treatment period due to a serious AE unrelated to study drug. Inadequate study drug adherence might have played a role in the virologic failure. No patients with baseline resistance-associated variants experienced virologic failure.

No patients in this study discontinued treatment and the reported side effects were largely similar to those seen in patients with normal renal function. The exception was anemia, which occurred in a substantially higher proportion of patients than was seen in the phase 3 studies of this regimen. However, hemoglobin declines are not unexpected because patients with ESRD have pre-existing anemia due to insufficient erythropoietin production and have limited ability to excrete RBV, leading to hemolysis. Due to the known impact of ESRD on RBV excretion, the dose of RBV was reduced to 200 mg/d, with provisions to discontinue RBV if hemoglobin levels met prespecified thresholds. Despite the reduced starting dose of RBV in this study, 9 of the 13 patients who received RBV met these thresholds and discontinued RBV. Most hemoglobin declines occurred in the first month of treatment. In addition to RBV interruption, erythropoietin was used in 4 of these patients, although no patient received blood transfusion.

Hematologic toxicity is of particular importance in this patient population characterized by a high prevalence of cardiovascular comorbidities.[11,30,31] One death occurred in this cohort, in a 60-year-old man with hypertensive nephropathy on hemodialysis who experienced hypertensive urgency and cardiomyopathy shortly after completing his 12-week course of treatment. Although the events leading to this patient's death were not related to the use of RBV or DAAs, this case and others reported with other DAA regimens highlight the fragile nature of these patients and the need for careful selection of patients who would benefit from HCV treatment, as well as the need for close monitoring during treatment.[32] Close collaboration between HCV-treating clinicians and a nephrologist may be needed to ensure that HCV treatment can be delivered safely and effectively.

Treatment of HCV in patients with severe renal disease should rely on DAAs that are not predominantly renally cleared to avoid accumulation of drug and/or metabolites. Unlike most DAAs, the metabolite of the nucleotide analogue NS5B polymerase inhibitor sofosbuvir is primarily cleared by the kidney, resulting in exposures 1280% higher when dosed 1 hour before hemodialysis and 2070% higher when dosed 1 hour after hemodialysis in patients with ESRD.[33] As a result, no dosage recommendation is given for sofosbuvir in patients with eGFR <30 mL/min/1.73 m^2.[33,34] Although most other DAAs are metabolized by the liver, increased drug exposures have been reported with simeprevir and daclatasvir in patients with severe renal impairment.[35,36]

Ombitasvir, paritaprevir, ritonavir, and dasabuvir are all metabolized by the liver, and phase 1 studies demonstrated that no dose adjustments are needed in patients with mild, moderate, or severe renal impairment.[28] Drug exposures of the DAAs in this study were within the range of levels observed in 1278 patients without stage 4 or 5 CKD included in phase 3 studies of this regimen. Additionally, intensive pharmacokinetic analyses of the 3 DAAs and ritonavir in a limited number of patients suggest that hemodialysis does not extract any of these drugs from the blood and is not a significant clearance pathway for this regimen. Study drugs could be administered without regard to the timing of hemodialysis. With an RBV dose roughly one-fifth the normal starting dose, RBV levels were 27%–36% lower than those observed in patients with normal renal function.

Clinical studies evaluating the efficacy of DAA-based HCV regimens are sparse in patients with severe CKD or ESRD. The investigational regimen of elbasvir and grazoprevir achieved SVR12 in 115 of 122 (94.3%) GT1-infected patients with stage 4 or 5 CKD, including patients on hemodialysis with prior treatment experience and with cirrhosis, and was well tolerated.[32] Conclusions in patients with cirrhosis ($n = 6$) may require further study. There are fewer data available on the use of other DAA regimens in this population.

Limitations of cohort 1 of this study include the small sample size and exclusion of patients with prior HCV treatment failure or with cirrhosis, both of which have historically had poorer response to therapy with IFN-based regimens and some DAA regimens. Treatment-experienced patients were excluded in cohort 1 of this study because the majority of HCV-infected adults with severe renal disease were likely to be treatment-naïve due to the poor tolerability of pegylated IFN/RBV in patients with renal insufficiency. In addition, the mean hemoglobin level at study outset was 12 g/dL, which makes these patients better able to tolerate RBV-induced decreases in hemoglobin compared with patients with more significant baseline anemia. Therefore, this study does not provide guidance for CKD patients with much lower baseline hemoglobin levels, who might not tolerate even a small decrease. Alternative RBV dosing schedules and RBV-free arms for patients with HCV GT1a were not assessed in cohort 1 of this study. Continued study of this regimen is warranted to determine whether the safety findings in this study are generalizable to a larger number of patients.

The results of this study are important for hepatologists, gastroenterologists, and infectious disease specialists who are accustomed to treating HCV-infected patients with DAA therapy but who may not yet have seen sufficient data to initiate DAA therapy in patients with ESRD. Nephrologists, who may not be accustomed to treating HCV, should also be aware that treatment options may now be available that can help prevent the end-stage sequelae of HCV. How treatment of HCV infection affects early or intermediate stages of CKD and how achievement of SVR impacts strategies for kidney transplantation in patients with ESRD require more study.

In conclusion, this study demonstrated that OBV/PTV/r + DSV ± RBV for 12 weeks was efficacious in a preliminary cohort of patients with HCV GT1 infection and stage 4 or 5 CKD, including those on hemodialysis. Treatment was well tolerated, as evidenced by high adherence to

medication and ability to complete the study without discontinuation due to AE. Hemoglobin declines were frequent and managed with interruption of RBV and administration of erythropoietin as needed, but did not appear to affect efficacy. Cohort 2 of this study will investigate additional GT1-infected patients, including pegylated IFN/RBV treatment-experienced patients and those with compensated cirrhosis.

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.2016.02.078.

References

1. Mohd Hanafiah K, Groeger J, Flaxman AD, et al. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013;57:1333–1342.
2. Hepatitis C information for health professionals. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm. Accessed June 2, 2014.
3. Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010;138:513–521, 521 e1–e6.
4. Okoh EJ, Bucci JR, Simon JF, et al. HCV in patients with end-stage renal disease. Am J Gastroenterol 2008; 103:2123–2134.
5. Bergman S, Accortt N, Turner A, et al. Hepatitis C infection is acquired pre-ESRD. Am J Kidney Dis 2005; 45:684–689.
6. Jadoul M, Poignet JL, Geddes C, et al. The changing epidemiology of hepatitis C virus (HCV) infection in haemodialysis: European multicentre study. Nephrol Dial Transplant 2004;19:904–909.
7. Sivapalasingam S, Malak SF, Sullivan JF, et al. High prevalence of hepatitis C infection among patients receiving hemodialysis at an urban dialysis center. Infect Control Hosp Epidemiol 2002;23:319–324.
8. Fabrizi F, Takkouche B, Lunghi G, et al. The impact of hepatitis C virus infection on survival in dialysis patients: meta-analysis of observational studies. J Viral Hepat 2007;14:697–703.
9. Lee JJ, Lin MY, Chang JS, et al. Hepatitis C virus infection increases risk of developing end-stage renal disease using competing risk analysis. PLoS One 2014; 9:e100790.
10. Satapathy SK, Lingisetty CS, Williams S. Higher prevalence of chronic kidney disease and shorter renal survival in patients with chronic hepatitis C virus infection. Hepatol Int 2012;6:369–378.
11. Goodkin DA, Bragg-Gresham JL, Koenig KG, et al. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). J Am Soc Nephrol 2003;14:3270–3277.
12. Morales JM, Bloom R, Roth D. Kidney transplantation in the patient with hepatitis C virus infection. Contrib Nephrol 2012;176:77–86.
13. Fabrizi F, Dulai G, Dixit V, et al. Meta-analysis: interferon for the treatment of chronic hepatitis C in dialysis patients. Aliment Pharmacol Ther 2003;18:1071–1081.
14. Russo MW, Goldsweig CD, Jacobson IM, et al. Interferon monotherapy for dialysis patients with chronic hepatitis C: an analysis of the literature on efficacy and safety. Am J Gastroenterol 2003;98:1610–1615.
15. Rebetol (ribavirin USP) capsules, for oral use [package insert]. Whitehouse Station, NJ: Merck. Revised on May 2015.
16. Bunchorntavakul C, Maneerattanaporn M, Chavalitdhamrong D. Management of patients with hepatitis C infection and renal disease. World J Hepatol 2015;7:213–225.
17. Copegus (ribavirin) Tablets [package insert]. South San Francisco, CA: Genentech. Revised on August 2011.
18. Pawlotsky JM. New hepatitis C therapies: the toolbox, strategies, and challenges. Gastroenterology 2014; 146:1176–1192.
19. Ferenci P. Treatment of hepatitis C in difficult-to-treat patients. Nat Rev Gastroenterol Hepatol 2015;12: 284–292.
20. Guidance for Industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm225333.pdf. Accessed September 1, 2015.
21. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1594–1603.
22. Andreone P, Colombo MG, Enejosa JV, et al. 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. Gastroenterology 2014;147:359–365.
23. **Ferenci P, Bernstein D**, Lalezari J, et al. ABT-450/r–ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014;370:1983–1992.
24. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370:1973–1982.
25. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1604–1614.
26. Rustgi V, Wedemeyer H, Pockros P, et al. Sustained virologic response rate of 96% in HCV genotype 1a-infected patients treated with ombitasvir/paritaprevir/r and dasabuvir with ribavirin. Am J Gastroenterol 2015; 110:S862.
27. Jacobson IM, Dufour JF, Wedemeyer H, et al. 99.7% sustained virologic response rate in 369 HCV genotype 1b-infected patients treated with label-recommended regimen of ombitasvir/paritaprevir/r and dasabuvir with

or without ribavirin. Am J Gastroenterol 2015; 110:S850–S851.
28. Khatri A, Dutta S, Marbury TC, et al. The pharmacokinetics and safety of the direct acting antiviral regimen of ABT-450/r, ombitasvir with/without dasabuvir in subjects with mild, moderate and severe renal impairment compared to subjects with normal renal function. Hepatology 2014;60:320A.
29. Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) [package insert]. North Chicago, IL: AbbVie, Inc. Revised on October 2015.
30. Fabrizi F, Dixit V, Messa P. Impact of hepatitis C on survival in dialysis patients: a link with cardiovascular mortality? J Viral Hepat 2012;19:601–607.
31. Petta S, Maida M, Macaluso FS, et al. Hepatitis C virus infection is associated with increased cardiovascular mortality: a meta-analysis of observational studies. Gastroenterology 2016;150:145–155.e4.
32. Roth D, Nelson D, Bruchfeld A, et al. C-SURFER: grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease. Lancet 2015; 386:1537–1545.
33. Sovaldi (sofosbuvir) tablets, for oral use [package insert]. Foster City, CA: Gilead Sciences. Revised on August 2015.
34. Harvoni (ledipasvir and sofosbuvir) tablets [package insert]. Foster City, CA: Gilead Sciences. Revised on March 2015.
35. Ouwerkerk-Mahadevan S, Beumont-Mauviel M, Mortier S, et al. Evaluation of the pharmacokinetics and renal excretion of simeprevir in subjects with renal impairment. Drugs R D 2015;15:261–270.
36. Daklinza (daclatasvir) tablets, for oral use [package insert]. Princeton, NJ: Bristol-Myers Squibb. Revised on July 2015.

Author names in bold designate shared co-first authorship.

Received December 16, 2015. Accepted February 25, 2016.

Reprint requests
Address requests for reprints to: Eric Lawitz, MD, The Texas Liver Institute, University of Texas Health Science Center, San Antonio, Texas 78215. e-mail: lawitz@txliver.com; fax: 1-210-579-1252.

Acknowledgments
The authors thank the patients, their families, co-investigators, subinvestigators, and study coordinators for their role in the study, as well as AbbVie employees Tami Pilot-Matias, PhD, and Christine Collins, PhD, of Clinical Virology, and Diana Shuster, PhD, of AbbVie Clinical Pharmacokinetics and Pharmacodynamics. Medical writing support was provided by Douglas E. Dylla, PhD, of AbbVie.

Conflicts of interest
The authors disclose the following: PJ Pockros: Speaker/Consultant/Advisor: Gilead, AbbVie, Janssen, Bristol-Myers Squibb, Merck; Research support paid to Scripps Health: Gilead, AbbVie, Janssen, Bristol-Myers Squibb, Merck, Conatus, Roche Molecular, Intercept. KR Reddy: Advisor: Gilead, Bristol-Myers Squibb, AbbVie, Merck, Janssen; Research support funds paid to the University of Pennsylvania: Gilead, Bristol-Myers Squibb, AbbVie, Merck, Janssen. PS Mantry: Speaking/Consultant/Ad board/Research support: AbbVie, Merck, Gilead, Janssen, Salix, Onyx, Hyperion, Vital Therapies, Intercept, Mass Biologics, Santaris. M Bennett: Stock: AbbVie. MS Sulkowski: Grant/research support funds paid to Johns Hopkins University: AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck; Consultant/Advisor: AbbVie, Bristol-Myers Squibb, Cocrystal Pharma, Gilead, Janssen, Merck, Trek. DE Bernstein: Research Support: AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck; Consultant/Speaker: AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck. E Lawitz: Speaker: AbbVie, Bristol-Myers Squibb, Gilead, Janssen; Research/Grant Support: AbbVie, Achillion, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, Roche, Salix, Santaris Pharmaceuticals, Tacere, Theravance; Advisor: AbbVie, Achillion, Bristol-Myers Squibb, Enanta, Gilead, Janssen, Merck, Novartis, Santaris, Regulus, Theravance.
E Cohen, DE Cohen, NS Shulman, D Wang, A Khatri, M Abunimeh, T Podsadecki: Employees of AbbVie and may hold AbbVie stock or options.
AbbVie sponsored the study (NCT02207088), contributed to its design, collection, analysis, and interpretation of the data, and participated in the writing, review, and approval of the content of the manuscript. All authors had access to all relevant data. This article contains information on the investigational use of ombitasvir/paritaprevir/ritonavir and dasabuvir.

Funding
This study sponsored by AbbVie (NCT02207088).