

# Daclatasvir and Sofosbuvir Treatment of Decompensated Liver Disease or Post-Liver Transplant Hepatitis C Virus Recurrence in Patients With Advanced Liver Disease/Cirrhosis in a Real-World Cohort

Paul Kwo,<sup>1</sup> Michael W. Fried,<sup>2</sup> K. Rajender Reddy,<sup>3</sup> Consuelo Soldevila-Pico,<sup>4</sup> Saro Khemichian,<sup>5</sup> Jama Darling,<sup>2</sup> Phillippe J. Zamor,<sup>6</sup> Andrew A. Napoli,<sup>7</sup> Beatrice Anduze-Faris,<sup>7</sup> and Robert S. Brown Jr.<sup>8</sup>

We report the findings of an early access program providing treatment for chronic hepatitis C virus infection (any genotype) with daclatasvir and sofosbuvir with/without ribavirin to patients with Child-Pugh class C cirrhosis or prior liver transplant recipients with recurrent hepatitis C virus infection and advanced fibrosis/cirrhosis. Patients had <12-month life expectancies per the local investigator. Patients received daclatasvir 60 mg and sofosbuvir 400 mg once daily, with/without ribavirin, for 24 weeks. Sustained virologic response (SVR) at posttreatment week 12 (SVR12) was measured. Assessments adhered to local standards. One patient (prior Child-Pugh class C who improved to class B) enrolled by exemption was included in the overall data but not the class C cohort efficacy/safety data. Of the 77 treated patients, including 62 liver transplant recipients (genotype 1, n = 43, 69%; genotype 3, n = 16, 26%) and 14 patients with Child-Pugh class C cirrhosis (genotype 1, n = 4, 29%; genotype 3, n = 10, 71%), 63 (82%) completed treatment. SVR12 rates by modified intention-to-treat analysis (excluding nonvirologic failures lost to follow-up and withdrawal [consent/no reason]) in the overall, liver transplant, and Child-Pugh class C cohorts were 84% (n = 64/76), 90% (n = 56/62), and 62% (n = 8/13), respectively. Rates increased to 96% (n = 64/67), 97% (n = 56/58), and 89% (n = 8/9), respectively, in patients with available virologic data (including early discontinuations); 22/23 patients with genotype 3 (96%) achieved SVR12. Single cases of virologic nonresponse and relapse (both in liver transplant recipients with genotype 1) and viral breakthrough (Child-Pugh class C; genotype 3) occurred. Six patients died, 10 had adverse events leading to discontinuation, and 30 experienced serious adverse events. *Conclusion:* Daclatasvir plus sofosbuvir, with/without ribavirin, provided high SVR12 rates and was generally well tolerated in patients with life-threatening disease and high unmet needs. (*Hepatology Communications* 2018;2:354-363)

## Introduction

The all-oral combination of the nonstructural protein 5A inhibitor daclatasvir (DCV) and the nonstructural protein 5B inhibitor sofosbuvir (SOF) exhibits activity against all major hepatitis C virus

(HCV) genotypes.<sup>(1,2)</sup> DCV+SOF, with or without ribavirin (RBV), has provided high rates of sustained virologic response and was generally well tolerated in multiple phase 3 studies in patients infected with HCV and with challenging-to-treat disease characteristics, including posttransplant recurrence, advanced cirrhosis,

*Abbreviations:* AE, adverse event; ATU, Autorisation Temporaire d'Utilisation; DCV, daclatasvir; FCH, fibrosing cholestatic hepatitis; HCV, hepatitis C virus; LLOQ, lower limit of quantification; MELD, Model for End-Stage Liver Disease; mITT, modified intention-to-treat; RBV, ribavirin; SAE, serious adverse event; SOF, sofosbuvir; SVR, sustained virologic response.

Received August 31, 2017; accepted January 11, 2018.

Additional Supporting Information may be found at [onlinelibrary.wiley.com/doi/10.1002/hep4.1156/full](https://onlinelibrary.wiley.com/doi/10.1002/hep4.1156/full).

Supported by Bristol-Myers Squibb.

genotype 3 infection, and coinfection with human immunodeficiency virus.<sup>(3-7)</sup> DCV+ SOF is now one of the regimens recommended by major treatment guidelines.<sup>(8,9)</sup>

Real-world early access initiatives ahead of local marketing authorizations can provide treatment options to patients with underlying disease characteristics who would likely be excluded from clinical studies. Globally, approximately 7,000 patients with chronic HCV infection have received treatment with DCV through such early access initiatives. The majority had advanced underlying disease, including decompensated cirrhosis, hepatocellular carcinoma, and/or posttransplant HCV recurrence. Real-world data collected in Europe from patients treated under these initiatives have been published.<sup>(10-12)</sup>

We present the final data from an early access program conducted in the United States in which patients with advanced disease received treatment with DCV+SOE±RBV. Patients with any HCV genotype and decompensated cirrhosis or severe posttransplant HCV recurrence with cirrhosis, advanced fibrosis, or fibrosing cholestatic hepatitis (FCH), were eligible to enroll. There were no approved oral direct-acting antiviral regimens at the time of the initiation of this program other than SOE+RBV.

## Participants and Methods

### PROGRAM DESIGN AND TREATMENT

This early access program (NCT01474811) was conducted in partnership with the HCV-TARGET consortium, whose methodologies in studies unrelated to this program have been reported.<sup>(13-17)</sup>

This early access program enrolled adults aged ≥18 years who had chronic HCV infection (any genotype) and decompensated Child-Pugh class C cirrhosis or were prior liver transplant recipients with recurrent HCV infection and advanced fibrosis/cirrhosis (Metavir F3-F4) or FCH. All patients had life expectancies of less than 12 months at the time of enrollment as assessed by the investigator, in accordance with general guidance for compassionate use programs in the United States. There were no Model for End-Stage Liver Disease (MELD) score restrictions at enrollment. Patients with creatinine clearance ≤30 mL/minute or clinical or pathologic evidence of acute ongoing liver graft rejection, women who were pregnant, and women of child-bearing potential not using appropriate contraception were excluded.

Copyright © 2018 The Authors. *Hepatology Communications* published by Wiley Periodicals, Inc., on behalf of the American Association for the Study of Liver Diseases. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs License](#), which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

View this article online at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).

DOI 10.1002/hep4.1156

*Potential conflict of interest:* Dr. Kwo has advisory arrangements with Bristol-Myers Squibb, Abbott, AbbVie, Gilead, Merck, Conatus, CVS, and Intercept and has received research grants/contracts from Bristol-Myers Squibb, AbbVie, Merck, Gilead, and Conatus. Dr. Fried has received consulting fees and research grants/contracts from AbbVie, Bristol-Myers Squibb, Gilead, and Merck. Dr. Reddy has received consulting fees and research grants/contracts paid to the University of Pennsylvania from Merck, AbbVie, Gilead, and Bristol-Myers Squibb and has received consulting fees from Janssen. Dr. Khemichian has received speakers' bureau payments from Gilead, Merck, and Bristol-Myers Squibb. Dr. Zamor has received speakers' bureau payments and research grants/contracts from Gilead, Merck, and AbbVie. Dr. Napoli and Dr. Anduze-Faris are employees and shareholders of Bristol-Myers Squibb. Dr. Brown Jr. has received consulting fees and research grants/contracts from Bristol-Myers Squibb, Gilead, and AbbVie. Dr. Soldevila-Pico and Dr. Darling report no conflicts of interest.

### ARTICLE INFORMATION:

From the <sup>1</sup>Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Palo Alto, CA; <sup>2</sup>Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC; <sup>3</sup>Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, PA; <sup>4</sup>Department of Medicine, College of Medicine, University of Florida, Gainesville, FL; <sup>5</sup>Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA; <sup>6</sup>Division of Hepatology, Carolinas Medical Center, Charlotte, NC; <sup>7</sup>Bristol Myers-Squibb, Lawrenceville, NJ; and <sup>8</sup>Department of Medicine, Weill Cornell Medicine, New York, NY.

### ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Paul Kwo, M.D.  
Division of Gastroenterology and Hepatology  
Stanford University School of Medicine  
750 Welch Road, Suite 210

Palo Alto, CA 94304  
E-mail: [pkwo@stanford.edu](mailto:pkwo@stanford.edu)  
Tel: +1-650-498-6080

Patients were enrolled at 15 Target-HCV centers in the United States from August 2014 to October 2015 and were to receive DCV 60 mg and SOF 400 mg once daily for 24 weeks. The addition of RBV was permitted at the discretion of the treating physician following consultation with the program medical monitor. After the treatment, patients entered follow-up for 24 weeks. DCV dose adjustments were permitted where drug-drug interactions were predicted and no alternative concomitant medication was available; once-daily doses of DCV were reduced to 30 mg when given with strong inhibitors of cytochrome P450 3A4 and/or P-glycoprotein and increased to 90 mg when given with moderate inducers of cytochrome P450 3A4 or P-glycoprotein. P-glycoprotein substrates with a narrow therapeutic index and substrates of organic anion-transporting polypeptide 1B1/B3 and breast cancer resistance protein were co-administered with caution. Concomitant use of strong inducers of cytochrome P450 3A4 or P-glycoprotein, cytochrome P450 3A4 substrates with a narrow therapeutic index, and amiodarone were prohibited. Liver disease stage, cirrhosis, and presence of FCH were determined by the investigator per local practices.

All patients provided written informed consent prior to participation, and the program was conducted in accordance with the ethical principles described in the Declaration of Helsinki. The protocol was reviewed and approved at each site by the local institutional review board and ethics committee.

## EFFICACY AND SAFETY ASSESSMENTS

All assessments adhered to local standard-of-care guidelines for disease monitoring and follow-up and per the operational management of the HCV-TARGET consortium.<sup>(18)</sup> Visits to assess safety and collect blood samples for laboratory assessments were conducted at baseline, on-treatment weeks 4, 12, and 24, and posttreatment weeks 12 and 24. Serum HCV RNA was quantified at each center using local methods. Safety was assessed as adverse events (AEs), clinical laboratory abnormalities, serious adverse events (SAEs), AEs leading to discontinuation, and death. Patients were monitored throughout the program up to the posttreatment week 12 visit or within 30 days of discontinuation. All drug-related AEs were monitored until either resolution or stabilization.

## ENDPOINTS

The primary efficacy measure was the proportion of patients achieving sustained virologic response (SVR) at posttreatment week 12 (SVR12), defined as HCV RNA less than the lower limit of quantification (LLOQ), target detected or not detected, at posttreatment week 12 ( $\geq 64$  days after the end of treatment to account for regional standard-of-care assessments). SVR24 was also measured.

Virologic failure categories included relapse (HCV RNA  $>$  LLOQ at any posttreatment visit after HCV RNA  $<$  LLOQ, target detected or not detected, at end of treatment), virologic breakthrough (HCV RNA  $\geq$  LLOQ on-treatment after HCV RNA  $<$  LLOQ, target detected or not detected), and other on-treatment virologic failures (HCV RNA never  $<$  LLOQ). Safety endpoints included AEs (including transplant rejection), SAEs, discontinuations due to AEs, death, and clinical laboratory abnormalities.

## STATISTICAL ANALYSES

Enrollment was based on the clinical need for treatment rather than statistical considerations; thus, there was no powering to establish a treatment effect. The primary population for efficacy analyses (modified intention-to-treat [mITT]) included patients who had received  $\geq 1$  dose of the program regimen. Patients without virologic failure who were lost to follow-up (on treatment), withdrew informed consent, or withdrew for undocumented reasons were excluded; those with missing data (who died or who were lost to posttreatment follow-up) were imputed as treatment failures. Sensitivity analyses were also performed based on the intention-to-treat population (patients who received  $\geq 1$  dose) and on patients with available HCV RNA data at posttreatment week 12, excluding those with nonvirologic failure (as-observed population). Safety analyses were performed on the intention-to-treat population. Efficacy and safety measures were processed with descriptive statistics.

## Results

### PATIENTS

A total of 77 patients comprising 62 transplant recipients with recurrent HCV infection and advanced fibrosis (81%) and 14 patients with chronic HCV infection and decompensated Child-Pugh class C

TABLE 1. BASELINE DEMOGRAPHIC AND DISEASE CHARACTERISTICS

	Liver Transplant Cohort DCV+SOF ± RBV n = 62*	Decompensated Cirrhosis Cohort DCV+SOF ± RBV n = 14 <sup>†</sup>	Overall Study Population DCV+SOF ± RBV N = 77 <sup>‡</sup>
Age, median (range) years	61 (34-79)	61 (45-68)	61 (34-79)
Male subjects, n (%)	47 (76)	12 (86)	60 (78)
Race, n (%)			
White	51 (82)	13 (93)	65 (84)
Black/African American	6 (10)	1 (7)	7 (9)
Other	5 (9)	0	5 (7)
HCV RNA, median (range) log <sub>10</sub> IU/mL	6.3 (0-8)	5.5 (2-6)	6.2 (0-8)
HCV genotype, n (%)			
1	43 (69)	4 (29)	47 (61)
2	3 (5)	0	4 (5)
3	16 (26)	10 (71)	26 (34)
HCV treatment experienced, n (%)	36 (58)	7 (50)	43 (56)
Prior PEG-IFN/RBV failure, n (%)	27 (44)	7 (50)	34 (44)
Prior triple therapy failure, n (%)	6 (10)	0	6 (8)
Prior HCC, n (%)	19 (31)	1 (7)	20 (26)
Posttransplant decompensating event, n (%)	53 (86)	NA	68 (88)
Posttransplant diabetes, n (%)	25 (40)	NA	30 (39)
Prior FCH, n (%)	9 (15)	NA	9 (12)
Cirrhosis, n (%)	49 (79)	NA	64 (83)
MELD score, n (%)			
≤9	16 (26)	1 (7)	17 (22)
10-15	9 (15)	6 (43)	15 (20)
≥16	5 (8)	4 (29)	9 (12)
Not obtained	19 (31) <sup>§</sup>	3 (21)	22 (29) <sup>§</sup>
Albumin, median (range) g/dL	3.4 (1.7-4.7)	3.0 (2.0-3.7)	3.3 (1.7-4.7)
Total bilirubin, median (range) mg/dL	0.9 (0.3-15.3)	1.9 (1.0-7.5)	1.1 (0.3-15.3)
Creatinine, median (range) mg/dL	1.2 (0.7-2.1)	1.2 (0.7-2.2)	1.2 (0.7-2.2)
INR, median (range)	1.1 (0.9-1.5)	1.3 (1.0-2.3)	1.1 (0.9-2.6)
Platelets, median (range) × 10 <sup>9</sup> /L	117 (41-262)	71.5 (27-267)	112 (27-420)

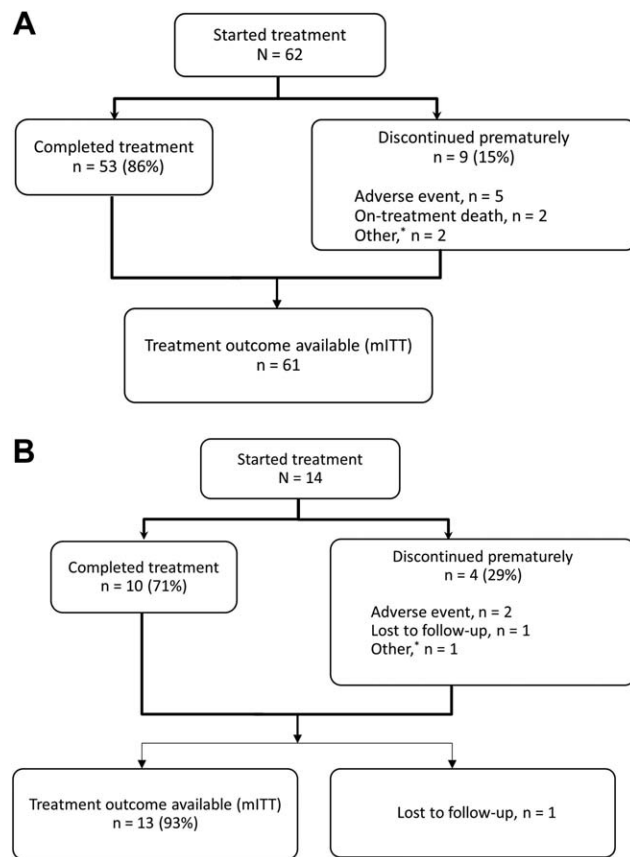
\*5 patients also received RBV; <sup>†</sup>3 patients received RBV; <sup>‡</sup>Includes 1 additional patient who had Child-Pugh class B cirrhosis at screening whose hepatic function had previously improved from Child-Pugh class C cirrhosis; <sup>§</sup>Does not include the records of 13 patients without cirrhosis.

Abbreviations: HCC, hepatocellular carcinoma; INR, international normalized ratio; PEG-IFN, pegylated interferon.

cirrhosis (18%) were enrolled and received treatment. One additional patient with Child-Pugh class B cirrhosis at screening, whose hepatic function had previously improved from Child-Pugh class C cirrhosis, was also included by a protocol exemption; data on this patient are included in the overall program demographic, safety, and efficacy summaries but not in individual cohort efficacy and safety summaries.

Among these 77 patients, median age was 61 (range, 34-79) years, and the majority were male (n = 60/77, 78%), Caucasian (n = 65/77, 84%), and prior HCV treatment recipients (n = 43/77, 56%). The most common HCV genotypes were 1a (n = 38/77, 49%) and 3 (n = 26/77, 34%); genotype 3 was more common among patients with decompensated Child-Pugh class C cirrhosis (n = 10/14, 71%) versus transplant recipients (n = 16/62, 26%). Median HCV RNA at baseline was 6.2 (range, 0-8) log<sub>10</sub> IU/mL. No patient was coinfecting with human immunodeficiency virus.

Baseline demographic and disease characteristics in the overall program population and individual patient cohorts are presented in Table 1. Patient histories were typically complex for patients with decompensated cirrhosis or liver transplant recipients with recurrent HCV infection and advanced fibrosis/cirrhosis or FCH. Markers of advanced liver disease were more frequently observed among patients with decompensated Child-Pugh class C cirrhosis versus transplant recipients, including platelets <100,000 × 10<sup>9</sup>/L (n = 9, 64% versus n = 21, 34% patients) and albumin <3.2 g/dL (n = 8, 57% versus n = 23, 37% patients); median MELD scores (where available) were also higher among patients with decompensated Child-Pugh class C cirrhosis (score 14, range, 8-25; n = 11) versus transplant recipients (score 9, range, 6-19; n = 30). By contrast, median creatinine levels were generally comparable between both cohorts, while rates of prior hepatocellular carcinoma were higher among transplant



**FIG. 1.** Patient disposition. (A) Posttransplant cohort. \*Insurance denied further treatment (n = 1), patient entered hospice care (n = 1). (B) Decompensated cirrhosis cohort. \*Liver transplant (n = 1).

recipients (31%; n = 19) versus patients with decompensated Child-Pugh class C cirrhosis (7%; n = 1). Among the transplant recipients, 4 were dual liver/kidney transplant recipients and 9 had FCH. All 4 dual transplant recipients had diabetes, 3 had cirrhosis, and all completed treatment; median creatinine clearance in these patients was 73.3 (range, 55.5-91.2) mL/minute/1.73 m<sup>2</sup>. Of the 9 patients with FCH, 3 had genotype 3 infection and 3 had hepatocellular carcinoma at the time of organ liver transplant, 4 had diabetes, and 1 was a dual kidney/liver transplant recipient. Further demographic details of the liver transplant recipients who were also kidney transplant recipients and/or had FCH are presented in [Supporting Table S1](#).

RBV was added to the treatment of 7 patients (9%), including 4 liver transplant recipients. Compared with patients not given RBV, recipients of RBV were more commonly infected with genotype 3

(n = 4/7, 57% versus n = 22/70, 31%), treatment experienced (n = 6/7, 86% versus n = 37/70, 53%), and had higher MELD ( $\geq 10$ ) scores (n = 5/7, 71% versus n = 20/70, 29%); all 3 RBV recipients with decompensated Child-Pugh class C cirrhosis were infected with genotype 3, were treatment experienced, and had MELD scores  $>10$ .

Immunosuppressant use among liver transplant recipients included tacrolimus (n = 41, 66%), cyclosporine (n = 15, 24%), everolimus/sirolimus (n = 7, 11%), and mycophenolate mofetil/mycophenolic acid (n = 24, 39%). Approximately half of the patients received tacrolimus, cyclosporine, or everolimus/sirolimus as monotherapy and half in combination with mycophenolate mofetil/mycophenolic acid.

Of the overall 77 patients enrolled into the program, 63 (82%) completed 24 weeks of treatment, while 14 (18%) discontinued early due to AEs (n = 10, including two deaths on treatment and four deaths during follow-up; see safety section for further detail), loss to follow-up (n = 1), liver transplantation (n = 1), denial of insurance for 12 additional weeks of SOF (n = 1; patient achieved SVR12), and preliminary approval of SOF only (n = 1; patient received SOF for only 4 days). Virologic outcome was available for 67 of 77 patients (87%), including 7 who discontinued. Patient dispositions stratified by cohort are presented in Fig. 1A,B.

## EFFICACY OUTCOMES

A total of 64/77 patients (83%) who received at least one dose of treatment (intention-to-treat population) achieved SVR12. Eighty-four percent (n = 64/76) of patients achieved SVR12 in the mITT population, including 90% of liver transplant recipients (n = 56/62) and 62% of patients with decompensated Child-Pugh class C cirrhosis (n = 8/13). The SVR12 rate increased to 96% (n = 64/67) when nonvirologic failures were excluded (as-observed analysis; Table 2), 97% among liver transplant patients (n = 56/58), and 89% among patients with decompensated Child-Pugh class C cirrhosis (n = 8/9). Observed SVR12 rates were  $\geq 95\%$  when nonvirologic failures were excluded, irrespective of HCV genotype, in the overall population (Table 2). Of the 26 patients with genotype 3 infection, 23 had virologic outcome data available; SVR12 was achieved by all 16 patients in the transplant cohort and 6/7 (86%) patients with decompensated Child-Pugh class C cirrhosis. One patient who also received RBV experienced viral breakthrough; 2 patients were lost to follow-up, and 1 received treatment for less

TABLE 2. EFFICACY OUTCOMES

	Transplant Cohort				Decompensated Cirrhosis			All Patients			
	HCV GT1	HCV GT2	HCV GT3	All	HCV GT1	HCV GT3	All	HCV GT1	HCV GT2	HCV GT3	All*
Started treatment, N	43	3	16	62	4	10	14	47	4	26	77
SVR12, n/N (%)											
mITT <sup>†</sup>	38/43 (88)	2/3 (67)	16/16 (100)	56/62 (90)	2/4 (50)	6/9 (67)	8/13 (62)	40/47 (85)	2/4 (50)	22/25 (88)	64/76 (84)
As observed	38/40 (95)	2/2 (100)	16/16 (100)	56/58 (97)	2/2 (100)	6/7 (86)	8/9 (89)	40/42 (95)	2/2 (100)	22/23 (96)	64/67 (96)
Nonresponder, n	1	0	0	1	0	0	0	1	0	0	1
Relapser, n	1	0	0	1	0	0	0	1	0	0	1
Viral breakthrough, n	0	0	0	0	0	1	1	0	0	1	1
Death, n	2	1	0	3	2	0	2	4	2	0	6
LTFU (on-treatment), n	0	0	0	0	0	0	1	0	0	1	1
LTFU (posttreatment), n	0	0	0	0	0	0	1	0	0	1	1
Treatment <1 week, n	1	0	0	1	0	1	1	1	0	1	2

\*Overall data include the patient with Child-Pugh class B cirrhosis at baseline (not included in cohort data); <sup>†</sup>Excludes lost to follow-up (on-treatment).

Abbreviations: GT, genotype; LTFU, lost to follow-up.

than 1 week. In the overall population, SVR12 was achieved by all 14 patients without cirrhosis and 81% (n = 39/48 [mITT]) of those with cirrhosis; the observed SVR12 in patients with cirrhosis was 95% (n = 39/41). Prior treatment experience status did not influence SVR12.

Virologic outcome was available in 6 of the 7 patients who received RBV, 5 of whom achieved SVR12, including 3 with genotype 3 infection. Of the 9 patients who had FCH in the overall population, 4 completed treatment, 3 discontinued early due to AEs (single cases of headache, pruritus, and sepsis [death]; none were related to treatment), and 2 discontinued for other reasons (insurance denial, preliminary approval of SOF only); overall outcomes were available for 9 patients, while virologic outputs were available for 7 patients, 6 of whom achieved SVR12. General improvements from baseline in MELD scores and bilirubin levels were observed (data not shown), and bilirubin normalization prior to the end of treatment was observed in 4 patients. All 4 patients in the overall population who were dual liver/kidney transplant recipients completed treatment, achieved SVR12, and had stable creatinine clearance rates; given the low number of these patients, caution should be used when interpreting these results. Among the 15 patients who discontinued, 6 liver transplant recipients who discontinued due to AEs (n = 4) or other reasons not reported (n = 2) achieved SVR12; treatment duration in these patients ranged from 69 to 166 days. Virologic breakthrough was observed in 1 patient; 2 were lost to follow-up either on treatment (n = 1) or posttreatment (n = 1).

## VIROLOGIC FAILURE

Virologic breakthrough was reported in 1 patient with decompensated Child-Pugh class C cirrhosis and genotype 3 infection who received DCV+SOF+RBV for 16 weeks. One case of nonresponse and one relapse (HCV RNA detected at posttreatment week 12 visit) were also observed in 2 liver transplant recipients treated with DCV+SOF for genotype 1 infection. Genotypic assessments of resistance-associated variants at baseline and at failure were not routinely assessed in this program.

## SAFETY

The program's safety profile reflected the severity of ongoing disease among patients with life expectancies of less than 12 months at enrollment (Table 3).

AEs were reported in 91% of patients overall (Table 3). The most common were nonspecific, such as fatigue, headache, and nausea. AEs were more common among patients receiving DCV+SOF+RBV therapy; however, few patients (n = 7) received this therapy and all had advanced liver disease. No AEs of graft transplant rejection were reported. Two patients receiving DCV+SOF therapy experienced an AE of acidosis. One patient experienced acidosis 1 day after discontinuing treatment due to pruritus; a second patient experienced acidosis within 7 days of experiencing an SAE of chronic renal failure. Neither patient had an AE of liver failure; however, both had some evidence of advancing liver disease/hepatic decompensation. There is no evidence or report that these events

TABLE 3. SAFETY

Parameter, n (%)	Posttransplant		Decompensated Cirrhosis		Overall N = 77*
	DCV+SOF n = 58	DCV+SOF+RBV n = 4	DCV+SOF n = 11	DCV+SOF+RBV n = 3	
AEs leading to discontinuation	6 (10)	1 (25)	2 (18)	0	10 (13) <sup>†</sup>
Serious adverse events	18 (31)	1 (25)	9 (82)	1 (33)	30 (39) <sup>‡</sup>
Deaths	2 (3)	1 (25)	2 (18)	0	6 (8) <sup>§</sup>
Any AEs	51 (88)	4 (100)	11 (100)	3 (100)	70 (91)
AEs in ≥10% of patients overall					
Fatigue	18 (31)	2 (50)	4 (36)	2 (67)	27 (35)
Headache	18 (31)	2 (50)	2 (18)	2 (67)	24 (31)
Nausea	15 (26)	2 (50)	3 (27)	3 (100)	23 (30)
Diarrhea	11 (19)	1 (25)	2 (18)	1 (33)	15 (19)
Asthenia	7 (12)	1 (20)	2 (18)	1 (33)	11 (14)
Hepatic encephalopathy	5 (9)	0	5 (45)	1 (33)	11 (14)
Abdominal pain	7 (12)	0	2 (18)	1 (33)	10 (13)
Insomnia	7 (12)	0	3 (27)	0	10 (13)
Tremor	2 (3)	0	4 (36)	3 (100)	9 (12)
Vomiting	5 (9)	1 (25)	2 (18)	2 (67)	10 (13)
Arthralgia	7 (12)	1 (25)	0	0	8 (10)
Renal failure acute	7 (12)	0	1 (9)	1 (33)	9 (12)

\*Includes one patient with a history of Child-Pugh class C cirrhosis who had Child-Pugh class B cirrhosis at screening and was enrolled by a protocol exception; patient is included in overall data but not individual cohort data (patient was a transplant recipient).

<sup>†</sup>Hemodialysis, headache, hepatorenal failure, pruritus, small-intestinal obstruction, death (hepatic failure), sepsis (all unrelated), renal failure (n = 2; one event was possibly treatment related); includes cardiac arrest in patient included as a protocol exception (event led to discontinuation and eventual death [unrelated]). <sup>‡</sup>Includes serious AE of cardiac arrest in patient enrolled as a protocol exception; serious AEs considered treatment related were hyperkalemia with acute renal failure in a single patient and renal failure in another patient.

<sup>§</sup>Includes cardiac arrest in patient enrolled as a protocol exception; hepatorenal syndrome, hepatic failure, sepsis, hepatocellular carcinoma, cardiac arrest (all unrelated), and multiorgan failure (possibly related).

were related to treatment (see [Supporting Table S3](#) for further details). AEs that occurred in more than 1 patient with FCH included headache (6 patients); urinary tract infection and pyrexia (4 patients each); pruritus, diarrhea, anxiety, and impaired memory (3 patients each); and hypertension, nausea, asthenia, nasopharyngitis, weight loss, back pain, tremor, and hepatic enzymes increased (2 patients each).

AEs led to the discontinuation of treatment in 10 of 77 patients (13%) overall and included headache, pruritus, small-intestinal obstruction, hemodialysis, renal failure (n = 2), hepatorenal failure, cardiac arrest, death due to hepatic failure, and sepsis (fatal). All AEs leading to discontinuation, except one event of renal failure, were considered unrelated to treatment, and three (headache, pruritus, and sepsis) occurred in patients with FCH.

SAEs, which occurred in 30 patients (39%), were more frequent among patients with decompensated Child-Pugh class C cirrhosis (n = 10/14, 71%) versus transplant recipients (n = 19/62, 31%). SAEs considered treatment related were hyperkalemia with acute renal failure in 1 liver transplant recipient (who recovered from both events) and renal failure in 1 patient with decompensated cirrhosis (resulting in death).

Most SAEs were directly or indirectly related to ongoing advanced liver disease.

Five patients enrolled per protocol died during treatment (n = 1) or during follow-up after discontinuation for AEs (n = 4); these patients' demographics and medical histories are presented in [Supporting Table S2](#). All 5 patients enrolled per protocol had decompensated liver disease, 2 of whom were also liver transplant recipients. In addition, the patient who was enrolled as a protocol exemption also died during treatment after experiencing an SAE of cardiac arrest.

## Discussion

This U.S. early access program provided clinically relevant real-world data describing the effectiveness and safety of DCV+SOF±RBV in challenging-to-treat patients with advanced liver disease. The program was designed and conducted in partnership with the HCV-TARGET consortium (NCT01474811), which has recently published several articles unrelated to this study describing the effectiveness and safety of SOF-containing direct-acting antiviral-only regimens in patients with HCV infection treated in real-world settings.<sup>(13-17)</sup> This unique program design permitted the

use of existing infrastructure to facilitate the protocol without third-party clinical research support and provision of access to DCV to highly experienced investigators offering potentially beneficial treatment to patients who were most in need.

The overall mITT response rate to DCV+SOF±RBV in this cohort, following a nominal treatment period of 24 weeks, was 84%, which is comparable to 24-week European mITT data for this regimen in patients with advanced liver disease from the European Union Compassionate Use Program (EU-CUP)<sup>(12)</sup> and the French Authorisation Temporaire d'Utilisation (ATU) early access program.<sup>(19)</sup>

The majority of treatment failures were for liver-associated deaths or discontinuations due to AEs rather than virologic failure. When nonvirologic treatment failures were excluded, only 3 of 67 patients experienced virologic failure. SVR12 rates among the patients with decompensated Child-Pugh class C cirrhosis and liver transplant recipients in the as-observed analyses were 89% (n = 8/9) and 97% (n = 56/58), respectively. Most patients with decompensated Child-Pugh class C cirrhosis (71%) had genotype 3 infection, consistent with the perceived unmet need for this population. Both the mITT and as-observed SVR12 rates for patients with decompensated Child-Pugh class C cirrhosis were consistent with the mITT (67%) and as-observed (80%) rates observed among a small (n = 6) sample of patients with Child-Pugh class C cirrhosis and genotype 3 infection in the French ATU program.<sup>(19)</sup> Overall SVR12 among genotype 3-infected patients from both cohorts was 88% (mITT; 96% as-observed), which is also consistent with data for genotype 3-infected patients in both the ATU and EU-CUP cohorts.

It is not possible to evaluate the impact of RBV on response in this data set due to the small number of patients and their nonrandomized allocation. However, the lower mITT response rate with or without RBV among patients with decompensated Child-Pugh class C cirrhosis (62%) versus liver transplant recipients (90%) is consistent with the 50% intention-to-treat rate of SVR12 among patients with Child-Pugh class C cirrhosis who received 12 weeks of DCV+SOF+RBV in the Phase III Daclatasvir, Sofosbuvir, and Ribavirin in Cirrhotic Participants and Participants Post-liver Transplant (ALLY-1) study, although there were differences in length of therapy and use of ribavirin.<sup>(5)</sup>

Among the 9 patients with FCH, 6 of 7 patients with available virologic outcomes achieved SVR12; 1 patient was a nonresponder. In the Compassionate

Use of Protease Inhibitors in Viral C Liver Transplantation (CUPILT) study, all 15 liver transplant recipients with FCH who received DCV+SOF achieved SVR12.<sup>(20)</sup>

Overall, DCV+SOF±RBV was well tolerated, and no unique safety events were reported despite the high proportion of patients with advanced liver disease. The majority of SAEs were directly or indirectly related to ongoing advanced liver disease, while the majority of SAEs and discontinuations were attributable to ongoing disease progression. The majority of deaths during this program were not related to treatment, and all the deceased patients had histories of decompensated liver disease along with other comorbidities. Safety outcomes were generally similar between patients with decompensated Child-Pugh class C cirrhosis and liver transplant recipients.

Limitations of this program were similar to that of most real-world observations. These included non-randomized treatment allocation, the use of RBV at the physicians' discretion (resulting in imbalanced sample sizes that complicated assessments of RBV), limited requirements for data capture (that may have led to under-reporting of safety events), and the lack of an analysis of baseline resistance-associated variants and their impact on the virologic outcome. However, despite these limitations, the study cohorts represent challenging-to-treat populations with advanced liver disease treated with an all-oral direct-acting antiviral combination in a real-world setting. The findings are consistent with the results of clinical trials evaluating DCV+SOF±RBV, despite the inclusion of a broad spectrum of patients that registration trials do not commonly capture, such as patients with Child-Pugh class C cirrhosis with genotype 3 infection.

Overall, these data from a patient population from the United States expand and corroborate the existing EU real-world compassionate use data for DCV+SOF±RBV in a small but more clinically advanced population comprising patients with decompensated Child-Pugh class C cirrhosis and posttransplant patients with advanced liver damage from HCV recurrence. Virologic failure was uncommon among both cohorts (one case of nonresponse and one relapse in transplant recipients with genotype 1 infection, and one case of viral breakthrough in a patient with decompensated cirrhosis and genotype 3 infection who received DCV+SOF+RBV for 16 weeks), and the majority of treatment failures, particularly among the patients with decompensated Child-Pugh class C cirrhosis, were due to AEs or death attributable to



ongoing baseline disease. This suggests that advanced pretransplant liver disease does not necessarily preclude a virologic response to DCV+SOF±RBV. Given the higher rate of nonvirologic failure in advanced decompensated cirrhosis, further study will be required to establish the risk–benefit balance of treating clinically advanced patients awaiting a transplant versus treating the posttransplant recurrence on a case-by-case basis, subject to the availability of donor organs. A recent study suggested that a preemptive strategy may be effective in patients with genotype 1 infection immediately posttransplant.<sup>(21)</sup>

Alternative treatment options in patients like those included in this program are limited. Paritaprevir- and elbasvir/grazoprevir-based regimens are not approved for the treatment of patients with decompensated cirrhosis. Similarly, elbasvir/grazoprevir and paritaprevir, ritonavir, and ombitasvir with or without dasabuvir or ribavirin are not approved in patients with posttransplant reinfection with either compensated or decompensated cirrhosis, respectively.<sup>(8)</sup> In addition, the combination of SOF with velpatasvir has not yet been studied in patients with Child-Pugh class C cirrhosis or transplant recipients,<sup>(22)</sup> and SOF in combination with ledipasvir is not a recommended regimen for the treatment of genotype 3 infection.<sup>(8)</sup> Taken collectively, these observations suggest that DCV+SOF±RBV may have advantages over other available regimens for the treatment of patients with advanced disease characteristics, such as advanced cirrhosis and/or posttransplant recurrence, especially in patients with genotype 3 infection. Furthermore, several of the next line of therapies that are likely to be approved may not offer further advantage in the treatment of such patients due to the inclusion of protease inhibitors, which are not recommended in patients with decompensated cirrhosis.<sup>(23)</sup>

In summary, DCV+SOF±RBV achieved high SVR12 rates and a favorable safety profile in a population of patients with life-threatening liver disease and high unmet needs.

*Acknowledgment:* We thank the participants and their families for their support and dedication and the following investigators and research staff at all study sites: Raymond Chung, Joseph Lim, Stuart Gordon, Shobha Joshi, Richard Sterling, Paul Gaglio, Arun Jesudian, Saro Khemichian, Jaime Aranda Michel, Devina Bhasin, Isabel Zacharias, and Paul Thuluvath. We thank the HCV-TARGET team and Bristol-Myers Squibb personnel for their support of

study execution: Angie Bauer, Lauren E Morelli, Joy A Peter, Monika Vainorius, Candace Mankowski, and Susan Hannah. Editorial support was provided by Dr. Andrew Stead at Articulate Science, funded by Bristol-Myers Squibb.

## REFERENCES

- 1) Gao M. Antiviral activity and resistance of HCV NS5A replication complex inhibitors. *Curr Opin Virol* 2013;3:514-520.
- 2) Sofia MJ, Bao D, Chang W, Du J, Nagarathnam D, Rachakonda S, et al. Discovery of a  $\beta$ -d-2'-deoxy-2'- $\alpha$ -fluoro-2'- $\beta$ -C-methyluridine nucleotide prodrug (PSI-7977) for the treatment of hepatitis C virus. *J Med Chem* 2010;53:7202-7218.
- 3) Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR, et al. Daclatasvir plus sofosbuvir for HCV in patients coinfecting with HIV-1. *N Engl J Med* 2015;373:714-725.
- 4) Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al.; ALLY-3 Study Team. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase 3 study. *Hepatology* 2015;61:1127-1135.
- 5) Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology* 2016;63:1493-1505.
- 6) Fontana RJ, Brown RS Jr, Moreno-Zamora A, Prieto M, Joshi S, Londoño MC, et al. Daclatasvir combined with sofosbuvir or simeprevir in liver transplant recipients with severe recurrent hepatitis C infection. *Liver Transpl* 2016;22:446-458.
- 7) Bunchorntavakul C, Reddy KR. Review article: the efficacy and safety of daclatasvir in the treatment of chronic hepatitis C virus infection. *Aliment Pharmacol Ther* 2015;42:258-272.
- 8) American Association for the Study of Liver Diseases, Infectious Diseases Society of America. HCV Guidance: recommendations for testing, managing, and treating hepatitis C. <http://www.hcvguidelines.org>. Accessed July 2017.
- 9) European Association for Study of Liver. EASL recommendations on treatment of hepatitis C 2015. *J Hepatol* 2015;63:199-236.
- 10) Coilly A, Fougerou-Leurent C, de Ledinghen V, Housset-Debry P, Duvoux C, Di Martino V, et al.; ANRS C023 CUPILT study group. Multicentre experience using daclatasvir and sofosbuvir to treat hepatitis C recurrence – the ANRS CUPILT study. *J Hepatol* 2016;65:711-718.
- 11) Leroy V, Hézode C, Métivier S, Tateo M, Conti F, Nguyen-Khac E, et al. Daclatasvir plus sofosbuvir with or without ribavirin in patients with HCV infection and decompensated cirrhosis: interim analysis of a French multicentre compassionate use programme [Abstract]. *J Hepatol* 2016;64(Suppl. 2):S829.
- 12) Welzel TM, Petersen J, Herzer K, Ferenci P, Gschwantler M, Wedemeyer H, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. *Gut* 2016;65:1861-1870.
- 13) Feld JJ, Maan R, Zeuzem S, Kuo A, Nelson DR, Di Bisceglie AM, et al. Effectiveness and safety of sofosbuvir-based regimens for chronic HCV genotype 3 infection: Results of the HCV-TARGET study. *Clin Infect Dis* 2016;63:776-783.

- 14) Welzel TM, Nelson DR, Morelli G, Di Bisceglie A, Reddy RK, Kuo A, et al.; HCV-TARGET Study Group. Effectiveness and safety of sofosbuvir plus ribavirin for the treatment of HCV genotype 2 infection: results of the real-world, clinical practice HCV-TARGET study. *Gut* 2017;66:1844-1852.
- 15) Sulkowski MS, Vargas HE, Di Bisceglie AM, Kuo A, Reddy KR, Lim JK, et al.; HCV-TARGET Study Group. Effectiveness of simeprevir plus sofosbuvir, with or without ribavirin, in real-world patients with HCV genotype 1 infection. *Gastroenterology* 2016;150:419-429.
- 16) Brown RS Jr, O'Leary JG, Reddy KR, Kuo A, Morelli GJ, Burton JR Jr, et al.; Hepatitis C Therapeutic Registry Research Network Study Group. Interferon-free therapy for genotype 1 hepatitis C in liver transplant recipients: Real-world experience from the hepatitis C therapeutic registry and research network. *Liver Transpl* 2016;22:24-33.
- 17) Terrault NA, Zeuzem S, Di Bisceglie AM, Lim JK, Pockros PJ, Frazier LM, et al.; HCV-TARGET Study Group. Effectiveness of ledipasvir-sofosbuvir combination in patients with hepatitis C virus infection and factors associated with sustained virologic response. *Gastroenterology* 2016;151:1131-1140.e5.
- 18) Sulkowski MS, Flamm S, Kayail Z, Lawitz EJ, Kwo P, McPhee F, et al. Short-duration treatment for chronic hepatitis C virus with daclatasvir, asunaprevir, beclabuvir, and sofosbuvir (FOURward study). *Liver Int* 2017;37:836-842.
- 19) Hézode C, Lebray P, De Ledinghen V, Zoulim F, Di Martino V, Boyer N, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, for hepatitis C virus genotype 3 in a French early access programme. *Liver Int* 2017;37:1314-1324.
- 20) Leroy V, Dumortier J, Coilly A, Sebah M, Fougerou-Leurent C, Radenne S, et al.; Agence Nationale de Recherches sur le SIDA et les Hépatites Virales CO23 Compassionate Use of Protease Inhibitors in Viral C in Liver Transplantation Study Group. Efficacy of sofosbuvir and daclatasvir in patients with fibrosing cholestatic hepatitis C after liver transplantation. *Clin Gastroenterol Hepatol* 2015;13:1993-2001.e1-e2.
- 21) Levitsky J, Verna EC, O'Leary JG, Bzowej NH, Moonka DK, Hyland RH, et al. Perioperative ledipasvir-sofosbuvir for HCV in liver-transplant recipients. *N Engl J Med* 2016;375:2106-2108.
- 22) Gilead Sciences I. EPCLUSA (sofosbuvir and velpatasvir) US Prescribing Information. June 2016. [www.gilead.com/~media/files/pdfs/medicines/liver-disease/epclusa/epclusa\\_pi.pdf](http://www.gilead.com/~media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.pdf). Accessed July 2017.
- 23) Bunchorntavakul C, Reddy KR. Treat chronic hepatitis C virus infection in decompensated cirrhosis - pre- or post-liver transplantation? The ironic conundrum in the era of effective and well-tolerated therapy. *J Viral Hepat* 2016;23:408-418.

## Supporting Information

Additional Supporting Information may be found at [onlinelibrary.wiley.com/doi/10.1002/hep4.1156/full](http://onlinelibrary.wiley.com/doi/10.1002/hep4.1156/full).