Supplementary Appendix

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

Supplement to: Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med. DOI: 10.1056/NEJMoa1512614

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Supplement to: Michael P. Curry, Jacqueline G. O'Leary, Natalie Bzowej, et al.
Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis

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Table S1. Reasons for screen failure

Screened Subjects	438
Screen Failure Subjects	170/438 (38.8%)
Screen Failure Subjects Who Did Not Meet Eligibility Criteria	164/170 (96.5%)
Inclusion Criterion 6: Confirmed CPT class B (7-9) at Screening	66/164 (40.2%)
Exclusion Criterion 13: Screening laboratory values not within acceptable ranges	63/164 (38.4%)
Exclusion Criterion 2: Inability to exclude HCC by imaging within 6 months of Day 1	24/164 (14.6%)
Inclusion Criterion 3: HCV RNA >= 10^4 IU/mL at Screening	12/164 (7.3%)
Inclusion Criterion 5: Cirrhosis determination as defined by the protocol	11/164 (6.7%)
Exclusion Criterion 15: Clinically-relevant alcohol or drug abuse within 12 months of screening	11/164 (6.7%)
Exclusion Criterion 1: History of clinically-significant illness or any other major medical disorder	7/164 (4.3%)
Exclusion Criterion 11: Active variceal bleeding within 6 months	3/164 (1.8%)
Exclusion Criterion 17: Use of any prohibited concomitant medications	3/164 (1.8%)
Exclusion Criterion 4: Screening ECG with clinically significant abnormalities	2/164 (1.2%)
Inclusion Criterion 1: Willing and able to provide written informed consent	1/164 (0.6%)
Inclusion Criterion 4: Chronic HCV infection	1/164 (0.6%)
Inclusion Criterion 11: Subject must be able to comply with the dosing instructions	1/164 (0.6%)
Exclusion Criterion 3: Infection with HBV or HIV	1/164 (0.6%)
Exclusion Criterion 10: Infection requiring systemic antibiotics at the time of screening	1/164 (0.6%)
Exclusion Criterion 16: Any contraindication to RBV therapy, per the approved package insert	1/164 (0.6%)
Exclusion Criterion 18: Known hypersensitivity to RBV, GS-5816, SOF or formulation excipients	1/164 (0.6%)
Screen Failure Subjects Who Met Eligibility Criteria	6/170 (3.5%)
Reasons for Non-Enrollment of Subjects Who Met Eligibility Criterion	
Withdrew Consent	2/6 (33.3%)
Adverse Event	1/6 (16.7%)
Lost to Follow-Up	1/6 (16.7%)
Other	1/6 (16.7%)
Outside of Visit Window	1/6 (16.7%)

Figure S1. Patient disposition

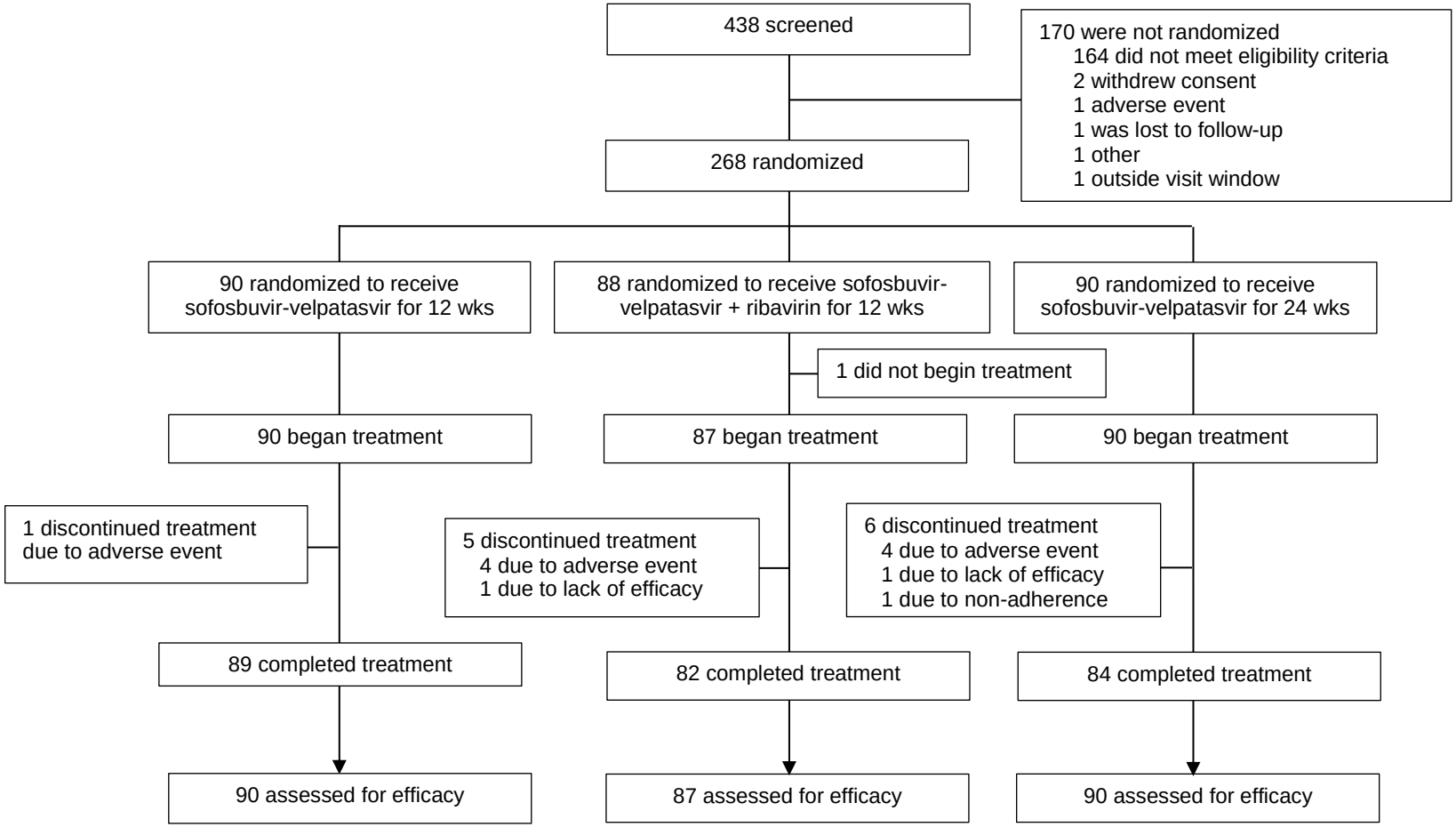

Table S2. Post-hoc comparison of SVR12 rates among treatment groups

	SOF/GS-5816 12 Weeks (N=90)	SOF/GS-5816+RBV 12 Weeks (N=87)	SOF/GS-5816 24 Weeks (N=90)
SVR12	75/90 (83.3%)	82/87 (94.3%)	77/90 (85.6%)
95% CI	74.0% to 90.4%	87.1% to 98.1%	76.6% to 92.1%
SOF/GS-5816+RBV 12 Weeks vs. SOF/GS-5816 24 Weeks			
p-value		0.056	
Prop Diff (98.3% CI)		8.7% (-2.2% to 19.6%)	
SOF/GS-5816 12 Weeks vs. SOF/GS-5816 24 Weeks			
p-value	0.68		
Prop Diff (98.3% CI)	-2.2% (-15.3% to 10.9%)		
SOF/GS-5816 12 Weeks vs. SOF/GS-5816+RBV 12 Weeks			
p-value	0.022		
Prop Diff (98.3% CI)	-10.9% (-22.3% to 0.4%)		

The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.
p-value for between group comparison is from the Cochran-Mantel-Haenszel test.

Table S3. Characteristics of patients with virologic failure

Group	Type of virologic failure	Age	Sex	Race	BMI	Geno-type	IL28B	HCV RNA	Timing	NS5A RAVs		NS5B RAVs
										Pretreatment	Post-treatment	Post-treatment
SOF-VEL for 12 wks	Relapse	55	F	White	22.6	3a	CT	5.9	PT wk 12	Y93H (>99%)	Y93H (>99%)	L320I (1%)
		58	M	White	28.6	1a	CT	5.1	PT wk 12	M28V (6%)	None	None
		57	M	White	28.6	3a	CT	6.2	PT wk 4	Y93H (5%)	Y93H (>99%)	None
		56	M	White	27.5	3a	CC	6.5	PT wk 12	None	Y93H (>99%)	None
		62	M	White	23.5	1a	CT	6.2	PT wk 4	None	None	None
		60	M	Black	34.6	1b	CT	6.4	PT wk4	Y93H (80%)	L31M (50%), L31V (50%), Y93H (>99%)	None
		57	M	White	31.4	3a	TT	5.6	PT wk 4	None	Y93H (>99%)	None
		48	M	White	55.6	3a	CT	6.3	PT4	None	Y93H (>99%)	None
		57	M	White	37.0	1a	CT	6.5	PT12	None	Y93N (>99%)	None
		57	M	White	27.7	3a	CT	6.0	PT4	None	Y93H (>99%)	None
		59	M	Black	37.2	1b	TT	6.1	PT12	L31I (8%), L31M (3%), Y93H (60%)	L31M (90%), L31V (10%), Y93H (>99%)	L159F (14%) S282T (4%)
SOF-VEL+RBV for 12 wks	Relapse	59	M	White	24.9	1a	CT	6.4	PT12	None	None	None
		48	M	White	29.5	3	CT	5.9	PT4	None	Y93H (>99%)	None
	Breakthrough	56	M	White	40.3	3a	TT	5.9	Wk 8	Y93H (3%)	Y93H (>99%)	N142T (3%) E237G (2%)
SOF-VEL for 24 wks	Relapse	61	M	Black	33.2	3a	CT	6.3	PT4	None	Y93H (>99%)	None
		58	M	White	34.2	3a	CT	6.2	PT4	None	Y93H (99%)	None
		57	M	White	32.5	3a	CT	6.3	PT4	None	Y93H (99%)	None
		60	M	White	47.4	1a	--	6.9	PT4	Q30H (65%), Y93H (57%), Y93N (1%)	Q30H (>99%), Y93H (>99%)	L159F (96%) S282T (3%)
		51	M	White	33.4	1b	TT	5.4	PT12	L31M (>99%)	L31M (98%), L31V (2%), Y93H (>99%)	None
		62	M	White	26.8	1a	CT	5.5	PT12	None	Q30R (95%), H58D (95%), Y93N (4%)	None
		53	F	White	41.4	3a	CC	6.0	PT4	None	M28T (2%), Y93H (>99%)	None
	Breakthrough	52	M	White	39.9	3a	CT	5.3	Wk 12	None	Y93H (98%)	E237G (2%)

Table S4. Adverse Events Leading to Discontinuation of Sofosbuvir-Velpatasvir

Treatment group	Adverse Event	Study Day	Relatedness*
Sofosbuvir-velpatasvir for 12 weeks	Diffuse large B-cell lymphoma	27	Not related
Sofosbuvir-velpatasvir + ribavirin for 12 weeks	Urinary tract infection	36	Not related
	Duodenal ulcer perforation	22	Not related
	Vomiting	80	Not related
	Ileus	31	Not related
Sofosbuvir-velpatasvir for 24 weeks	Hypotension, sepsis, spontaneous bacterial peritonitis, hepatorenal syndrome	35	Related
	Incarcerated umbilical hernia	28	Not related
	Acute myocardial infarction, acute kidney injury and acute respiratory failure	9	Not related
	Hyperbilirubinemia, jaundice	91	Not related

*In the opinion of the Investigator.

Table S5. Serious adverse events

	SOF/GS-5816 12 Weeks (N=90)	SOF/GS-5816+RBV 12 Weeks (N=87)	SOF/GS-5816 24 Weeks (N=90)
Number (%) of Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	17 (18.9%)	14 (16.1%)	16 (17.8%)
Number (%) of Subjects Experiencing Any Treatment-Emergent Serious Adverse Event by Preferred Term			
Hepatic encephalopathy	2 (2.2%)	2 (2.3%)	1 (1.1%)
Sepsis	1 (1.1%)	3 (3.4%)	1 (1.1%)
Gastrointestinal haemorrhage	3 (3.3%)	0	0
Hepatocellular carcinoma	0	0	3 (3.3%)
Hyponatraemia	1 (1.1%)	2 (2.3%)	0
Anaemia	1 (1.1%)	1 (1.1%)	0
Cellulitis	1 (1.1%)	1 (1.1%)	0
Escherichia infection	0	1 (1.1%)	1 (1.1%)
Gastric varices haemorrhage	1 (1.1%)	0	1 (1.1%)
Hip fracture	0	1 (1.1%)	1 (1.1%)
Nausea	2 (2.2%)	0	0
Seizure	1 (1.1%)	1 (1.1%)	0
Upper gastrointestinal haemorrhage	1 (1.1%)	0	1 (1.1%)
Urinary tract infection	0	2 (2.3%)	0
Acute myocardial infarction	0	0	1 (1.1%)
Adrenal insufficiency	0	0	1 (1.1%)
Ascites	0	1 (1.1%)	0
Atrial fibrillation	0	0	1 (1.1%)
Bacteraemia	0	1 (1.1%)	0
Bone abscess	1 (1.1%)	0	0
Cerebrovascular accident	0	0	1 (1.1%)
Colitis	1 (1.1%)	0	0
Depression	1 (1.1%)	0	0
Device related infection	0	1 (1.1%)	0
Diffuse large B-cell lymphoma	1 (1.1%)	0	0
Duodenal ulcer perforation	0	1 (1.1%)	0
Dyspnoea	0	1 (1.1%)	0
Fall	0	0	1 (1.1%)
Gastric ulcer	1 (1.1%)	0	0
Haematemesis	0	1 (1.1%)	0
Head injury	0	0	1 (1.1%)
Hepatorenal syndrome	0	0	1 (1.1%)
Hernia	1 (1.1%)	0	0
Hyperbilirubinaemia	0	0	1 (1.1%)
Hyperkalaemia	0	1 (1.1%)	0
Hypotension	0	0	1 (1.1%)
Hypoxia	0	0	1 (1.1%)
Ileus	0	1 (1.1%)	0
Incarcerated umbilical hernia	0	0	1 (1.1%)
Infectious colitis	0	1 (1.1%)	0
Iron deficiency anaemia	1 (1.1%)	0	0
Jaundice	0	0	1 (1.1%)
Joint dislocation	1 (1.1%)	0	0
Localised infection	1 (1.1%)	0	0
Mallory-Weiss syndrome	1 (1.1%)	0	0
Mental status changes	1 (1.1%)	0	0
Myocardial infarction	1 (1.1%)	0	0
Osteomyelitis	1 (1.1%)	0	0
Peritonitis	0	0	1 (1.1%)
Pleural effusion	0	1 (1.1%)	0
Pneumonia	0	0	1 (1.1%)
Portal vein thrombosis	1 (1.1%)	0	0
Pulmonary hypertension	0	0	1 (1.1%)
Radius fracture	0	0	1 (1.1%)
Rectal haemorrhage	0	0	1 (1.1%)
Respiratory failure	0	0	1 (1.1%)
Rhabdomyolysis	0	1 (1.1%)	0
Rib fracture	0	0	1 (1.1%)
Skin ulcer	0	1 (1.1%)	0
Small intestinal obstruction	1 (1.1%)	0	0
Splenic rupture	0	0	1 (1.1%)
Syncope	0	1 (1.1%)	0
Tibia fracture	0	0	1 (1.1%)
Traumatic haemothorax	0	0	1 (1.1%)
Vomiting	1 (1.1%)	0	0

Table S6. Deaths

Treatment group	Cause	Comments
SOF/VEL 12 weeks	Liver failure	The 55-year-old female subject underwent surgery for right hip fracture (due to alcohol-related fall) and subsequently deteriorated with hematomas, disseminated intravascular coagulation, and atrial fibrillation. The subject was placed in hospice and died of liver failure on posttreatment Day 86.
	Sepsis, multi-organ failure	The 58-year-old female subject died from sepsis with multi organ failure on posttreatment Day 35 during hospitalization for spontaneous bacterial peritonitis and pneumonia.
	Septic shock	The 59-year-old male subject declined medical treatment of osteomyelitis and subsequently developed septic shock resulting in death on posttreatment Day 65.
SOF/VEL + RBV 12 weeks	Sepsis	The 69-year-old male subject was hospitalized for a duodenal ulcer perforation with study drug discontinued on Day 22. There was a complicated hospitalization course with bacterial and fungal peritonitis, ischemic colitis, pneumoperitoneum, atrial fibrillation, and pneumonia, and the subject subsequently died of sepsis on posttreatment Day 15.
	Respiratory failure	The 65-year-old male subject died from respiratory failure on posttreatment Day 33 during hospitalization for hyponatremia and aspiration pneumonia.
	Cardiopulmonary arrest	The 51-year-old male subject was admitted with a diagnosis of alcoholic liver disease with ascites, hypercoaguable state, acute kidney disease, and hyponatremia. He subsequently developed cardiopulmonary arrest at which point he was placed in hospice care and died on posttreatment Day 147.
SOF/VEL 24 weeks	Acute myocardial infarction	The 52-year-old male subject suffered massive myocardial infarction leading to death. The subject was not on amiodarone. Cardiac risk factors were age, gender, and long-term smoking history.
	Liver failure	The 67-year-old male subject experienced incarcerated umbilical hernia leading to study drug discontinuation on Day 28 of treatment. There was a prolonged hospitalization course with eventual death from liver failure on posttreatment Day 39.
	Sepsis	The 53-year-old female subject died from sepsis with multi-organ failure on posttreatment Day 102 during hospitalization for spontaneous bacterial peritonitis and E coli bacteremia.

Figure S3. Selected Laboratory Parameters During Study Treatment