Supplementary Appendix

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

Supplement to: Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med. DOI: 10.1056/NEJMoa1512612

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Table S1. Reasons for screen failure: ASTRAL-2

	Total
Screened Subjects	317
Screen Failure Subjects	48/317 (15.1%)
Screen Failure Subjects Who Did Not Meet Eligibility Criteria	45/48 (93.8%)
Exclusion Criteria 3: Screening laboratory values not within acceptable ranges	18/45 (40.0%)
Inclusion Criteria 4: HCV genotype 2	8/45 (17.8%)
Exclusion Criteria 1: History of clinically-significant illness or any other major medical disorder	7/45 (15.6%)
Inclusion Criteria 3: HCV RNA >= 10^4 IU/mL at Screening	6/45 (13.3%)
Exclusion Criteria 8: Clinically-relevant alcohol or drug abuse within 12 months of screening.	6/45 (13.3%)
Inclusion Criteria 1: Willing and able to provide written informed consent	2/45 (4.4%)
Inclusion Criteria 8: Liver imaging within 6 months of Baseline/Day 1	2/45 (4.4%)
Inclusion Criteria 5: Chronic HCV infection	1/45 (2.2%)
Inclusion Criteria 7: Cirrhosis determination as defined by the protocol	1/45 (2.2%)
Inclusion Criteria 12: Subject must be of generally good health	1/45 (2.2%)
Exclusion Criteria 2: Screening ECG with clinically significant abnormalities	1/45 (2.2%)
Subjects Who Met Eligibility Criteria Who Were Screen Failed (or Not Randomized)	3/48 (6.3%)
Reasons for Non-Enrollment of Subjects Who Met Eligibility Criterion	
Lost to Follow-Up	1/3 (33.3%)
Outside of Visit Window	1/3 (33.3%)
Withdrew Consent	1/3 (33.3%)

Table S2. Reasons for screen failure: ASTRAL-3

	Total
Screened Subjects	652
Screen Failure Subjects	94/652 (14.4%)
Screen Failure Subjects Who Did Not Meet Eligibility Criteria	87/94 (92.6%)
Exclusion Criterion 3: Screening laboratory values not within acceptable ranges	34/87 (39.1%)
Exclusion Criterion 8: Clinically-relevant alcohol or drug abuse within 12 months of screening	18/87 (20.7%)
Exclusion Criterion 1: History of clinically-significant illness or any other major medical disorder	10/87 (11.5%)
Inclusion Criterion 4: HCV genotype 3	6/87 (6.9%)
Inclusion Criterion 13: Subject must be able to comply with the dosing instructions	5/87 (5.7%)
Inclusion Criterion 6: Classification as treatment naive or treatment experienced	4/87 (4.6%)
Inclusion Criterion 3: HCV RNA >= 10^4 IU/mL at Screening	3/87 (3.4%)
Inclusion Criterion 8: Liver imaging within 6 months of Baseline/Day 1	3/87 (3.4%)
Exclusion Criterion 5: Pregnant or nursing female or male with pregnant female partner	2/87 (2.3%)
Exclusion Criterion 9: Use of any prohibited concomitant medications	2/87 (2.3%)
Inclusion Criterion 9: Negative pregnancy tests for females of childbearing potential	2/87 (2.3%)
Exclusion Criterion 12: History of clinically significant hemoglobinopathy	1/87 (1.1%)
Inclusion Criterion 10: Agree to use protocol specified method(s) of contraception	1/87 (1.1%)
Inclusion Criterion 1: Willing and able to provide written informed consent	1/87 (1.1%)
Subjects Who Met Eligibility Criteria Who Were Screen Failed (or Not Randomized)	7/94 (7.4%)
Reasons for Non-Enrollment of Subjects Who Met Eligibility Criterion	
Withdrew Consent	6/7 (85.7%)
Study Enrollment Closed	1/7 (14.3%)

Figure S1. Patient disposition: ASTRAL-2

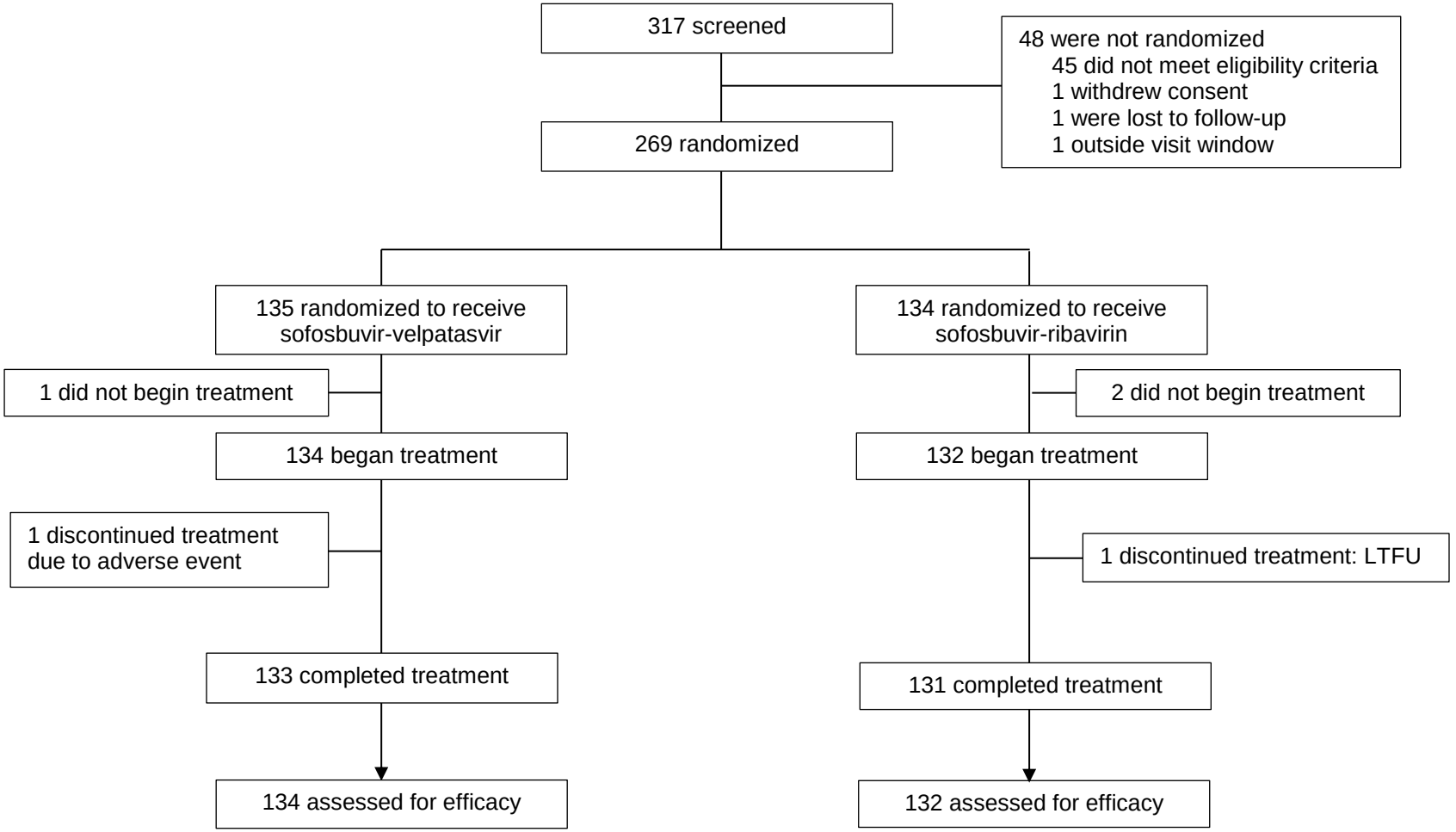

Figure S2. Patient disposition: ASTRAL-3

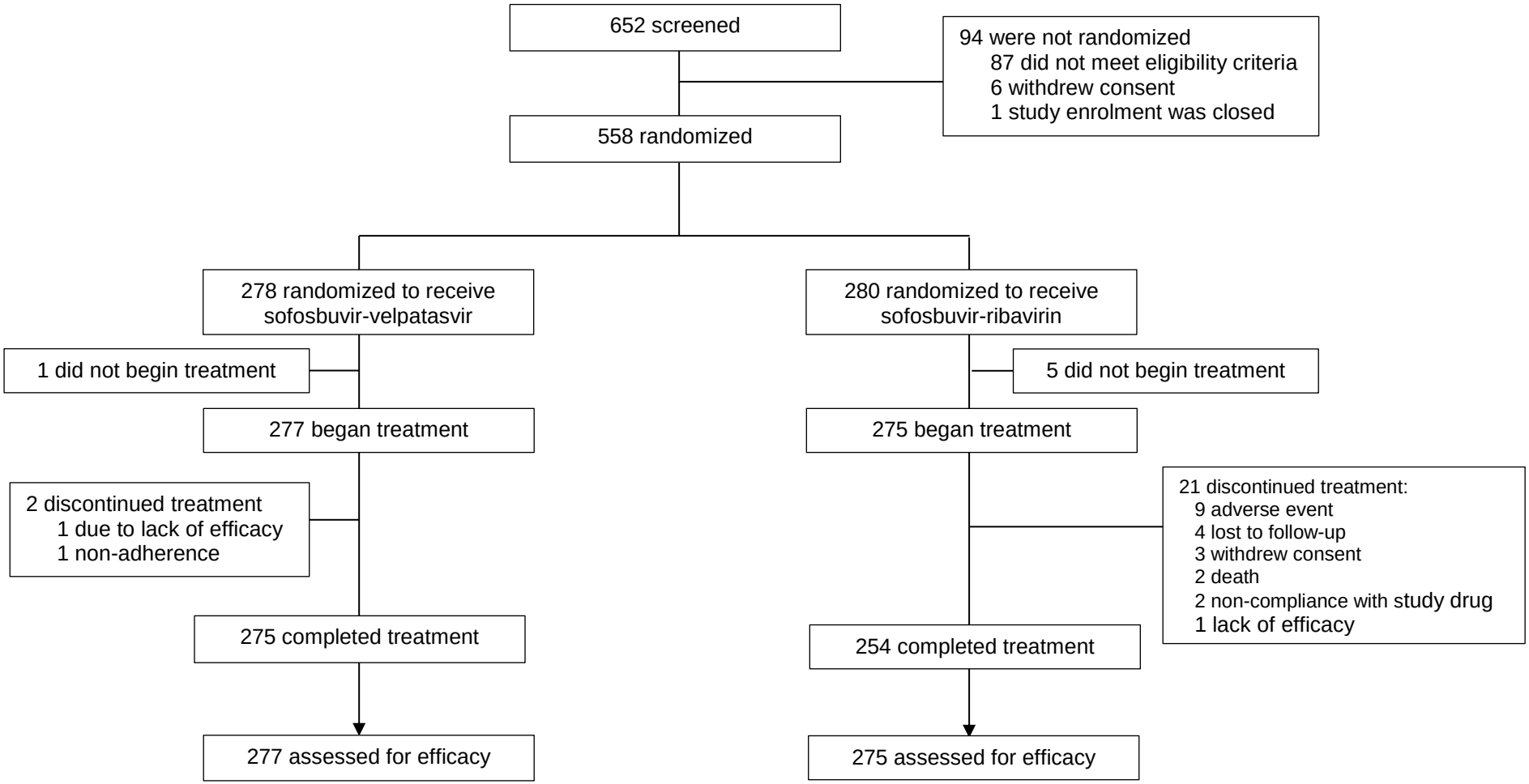

Table S3. SVR12 in patient subgroups of ASTRAL-3

	SOF/GS-5816 12 Weeks (N=277)	SOF+RBV 24 Weeks (N=275)	SOF/GS-5816 12 Weeks vs. SOF+RBV 24 Weeks
			Prop Diff (95% CI)
Overall	264/277 (95.3%)	221/275 (80.4%)	14.8% (9.6% to 20.0%)
95% CI	92.1% to 97.5%	75.2% to 84.9%	
Age at Baseline (Years)			
< 65	257/270 (95.2%)	210/261 (80.5%)	14.7% (9.3% to 20.4%)
95% CI	91.9% to 97.4%	75.1% to 85.1%	
>= 65	7/7 (100.0%)	11/14 (78.6%)	21.4% (-21.3% to 50.8%)
95% CI	59.0% to 100.0%	49.2% to 95.3%	
Sex at Birth			
Male	159/170 (93.5%)	132/174 (75.9%)	17.7% (10.1% to 25.4%)
95% CI	88.7% to 96.7%	68.8% to 82.0%	
Female	105/107 (98.1%)	89/101 (88.1%)	10.0% (3.2% to 18.1%)
95% CI	93.4% to 99.8%	80.2% to 93.7%	
Race			
White	238/250 (95.2%)	187/239 (78.2%)	17.0% (11.1% to 23.1%)
95% CI	91.8% to 97.5%	72.5% to 83.3%	
Black	3/3 (100.0%)	1/1 (100.0%)	0.0% (-70.8% to 97.5%)
95% CI	29.2% to 100.0%	2.5% to 100.0%	
Other	23/24 (95.8%)	32/34 (94.1%)	1.7% (-15.7% to 16.0%)
95% CI	78.9% to 99.9%	80.3% to 99.3%	
Baseline BMI (kg/m2)			
< 30	214/226 (94.7%)	174/214 (81.3%)	13.4% (7.4% to 19.7%)
95% CI	90.9% to 97.2%	75.4% to 86.3%	
>= 30	50/51 (98.0%)	47/61 (77.0%)	21.0% (8.8% to 33.7%)
95% CI	89.6% to 100.0%	64.5% to 86.8%	
HCV Genotype			
3a	253/265 (95.5%)	199/250 (79.6%)	15.9% (10.2% to 21.7%)
95% CI	92.2% to 97.6%	74.1% to 84.4%	
3b	2/2 (100.0%)	5/5 (100.0%)	0.0% (-84.2% to 52.5%)
95% CI	15.8% to 100.0%	47.8% to 100.0%	
3h	0/0	2/2 (100.0%)	
95% CI		15.8% to 100.0%	
3k	1/1 (100.0%)	0/0	
95% CI	2.5% to 100.0%		
3 (no confirmed subtype)	8/9 (88.9%)	15/18 (83.3%)	5.6% (-32.0% to 33.7%)
95% CI	51.8% to 99.7%	58.6% to 96.4%	
Cirrhosis			
Yes	73/80 (91.3%)	55/83 (66.3%)	25.0% (11.5% to 37.2%)
95% CI	82.8% to 96.4%	55.1% to 76.3%	
No	191/197 (97.0%)	163/187 (87.2%)	9.8% (4.2% to 15.7%)
95% CI	93.5% to 98.9%	81.5% to 91.6%	
Missing	0/0	3/5 (60.0%)	
95% CI		14.7% to 94.7%	

Table S3. SVR12 in patient subgroups of ASTRAL-3 (continued)

	SOF/GS-5816 12 Weeks (N=277)	SOF+RBV 24 Weeks (N=275)	SOF/GS-5816 12 Weeks vs. SOF+RBV 24 Weeks
			Prop Diff (95% CI)
IL28B			
CC	99/105 (94.3%)	89/111 (80.2%)	14.1% (4.3% to 23.4%)
95% CI	88.0% to 97.9%	71.5% to 87.1%	
Non-CC	165/172 (95.9%)	132/164 (80.5%)	15.4% (8.6% to 22.6%)
95% CI	91.8% to 98.3%	73.6% to 86.3%	
CT	143/148 (96.6%)	106/133 (79.7%)	16.9% (9.4% to 25.0%)
95% CI	92.3% to 98.9%	71.9% to 86.2%	
TT	22/24 (91.7%)	26/31 (83.9%)	7.8% (-12.6% to 26.6%)
95% CI	73.0% to 99.0%	66.3% to 94.5%	
Baseline HCV RNA (IU/mL)			
< 800,000	85/86 (98.8%)	72/81 (88.9%)	9.9% (2.8% to 18.9%)
95% CI	93.7% to 100.0%	80.0% to 94.8%	
>= 800,000	179/191 (93.7%)	149/194 (76.8%)	16.9% (9.9% to 24.0%)
95% CI	89.3% to 96.7%	70.2% to 82.5%	
Baseline ALT			
<= 1.5 x ULN	92/95 (96.8%)	73/87 (83.9%)	12.9% (3.9% to 22.6%)
95% CI	91.0% to 99.3%	74.5% to 90.9%	
> 1.5 x ULN	172/182 (94.5%)	148/188 (78.7%)	15.8% (8.8% to 22.9%)
95% CI	90.1% to 97.3%	72.2% to 84.3%	
Prior HCV Treatment Experience			
Treatment-Naive	200/206 (97.1%)	176/204 (86.3%)	10.8% (5.3% to 16.5%)
95% CI	93.8% to 98.9%	80.8% to 90.7%	
Treatment-Experienced	64/71 (90.1%)	45/71 (63.4%)	26.8% (12.2% to 40.1%)
95% CI	80.7% to 95.9%	51.1% to 74.5%	
Prior HCV Treatment			
DAA+Peg-IFN+RBV	1/1* 100.0%)	0/0	
95% CI	2.5% to 100.0%		
Peg-IFN+RBV	57/64 (89.1%)	41/65 (63.1%)	26.0% (9.8% to 40.3%)
95% CI	78.8% to 95.5%	50.2% to 74.7%	
Other	6/6 (100.0%)	4/6 (66.7%)	33.3% (-17.4% to 77.7%)
95% CI	54.1% to 100.0%	22.3% to 95.7%	
Prior HCV Treatment Response			
Non-Responder	17/20 (85.0%)	14/24 (58.3%)	26.7% (-1.2% to 51.8%)
95% CI	62.1% to 96.8%	36.6% to 77.9%	
Relapse/Breakthrough	47/51 (92.2%)	31/47 (66.0%)	26.2% (8.9% to 42.5%)
95% CI	81.1% to 97.8%	50.7% to 79.1%	

*One patient with HCV genotype 3 had previously received telaprevir with pegylated interferon and ribavirin.

Table S4. Characteristics of patients receiving sofosbuvir-velpatasvir who relapsed in ASTRAL-3

Age	Sex	Race	BMI	Geno-type	Cirrhosis	IL28B	HCV RNA	Timing of VF	HCV treatment history	Resistance-associated variants			
										NS5A		NS5B	
										BL	FU wk 12	BL	FU wk12
53	F	White	23.7	3a	Yes	CC	6.9	FU wk 4	Naive	Y93H (15.2%)	Y93H (>99%)	None	None
58	M	White	24.6	3a	Yes	CC	6.3	FU wk 12	Experienced	None	Y93H (>99%)	None	None
61	M	White	25.2	3a	Yes	CT	6.0	FU wk 12	Naïve	Y93H (>99%)	Y93H (>99%)	None	None
61	M	White	21.7	3a	No	TT	5.5	FU wk 4	Experienced	None	Y93H (>99%)	None	None
50	M	White	28.7	3a	No	CT	6.5	FU wk 4	Naïve	Y93H (>99%)	Y93H (>99%)	None	None
56	M	White	26.7	3a	Yes	TT	6.1	FU wk 4	Experienced	None	Y93H (>99%)	None	None
45	M	White	30.6	3	No	CC	6.9	FU wk 4	Experienced	Y93H (2.8%)	Y93H (>99%)	None	None
46	M	White	23.9	3a	Yes	CT	6.1	FU wk 4	Experienced	A30K (>99%)	A30K (>99%) Y93H (97.2%)	None	None
57	M	White	26.8	3a	Yes	CT	6.3	FU wk 4	Naïve	None	Y93H (>99%)	None	None
56	M	White	28.1	3a	Yes	CT	6.3	FU wk 4	Experienced	None	Y93H (>99%)	None	None
39	M	White	22.4	3a	No	CC	6.6	FU wk 12	Experienced	None	GT1a reinfection		

F denotes female; M male; BMI body mass index; VF virologic failure; BL baseline; FU follow-up.

Figure S3. Rates of sustained virologic response by baseline NS5A resistance-associated variants (1% cutoff) in ASTRAL-3

Legend: Figures show rates of SVR12 in patients with and without NS5A resistance-associated variants at baseline. Figure S3A shows results in patients with any NS5A resistance-associated variant. Figure S3B shows results in patients with the Y93H NS5A resistance-associated variant at baseline.

Figure S3A. Overall

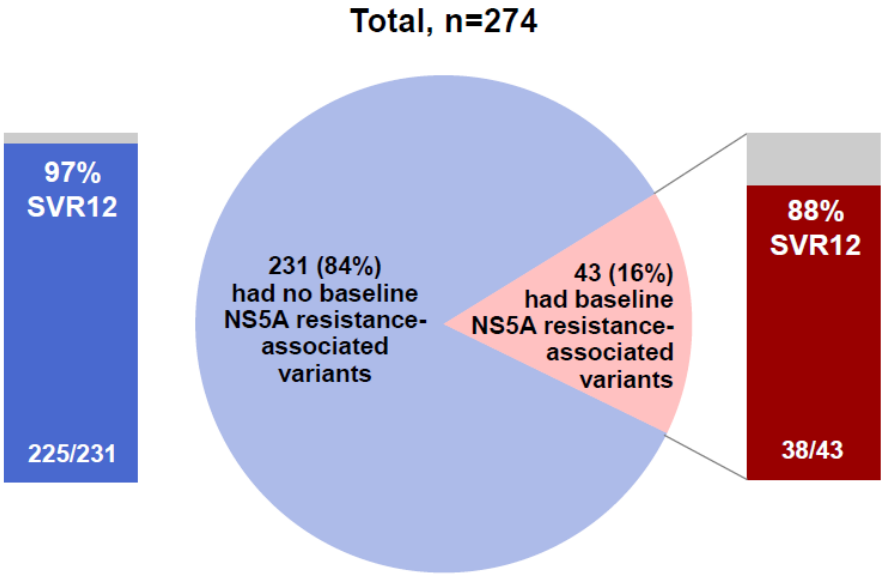

Figure S3B. By the Y93H NS5A resistance-associated variant (1% cutoff)

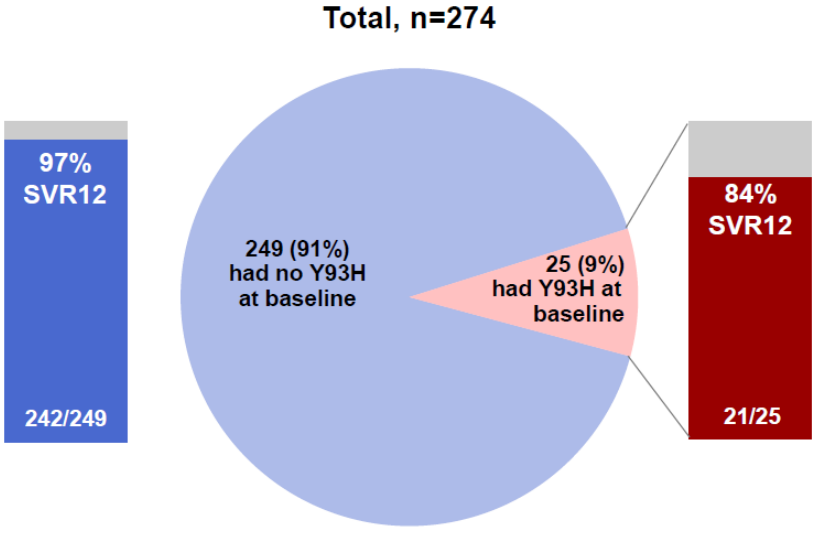

Table S5. Serious adverse events in ASTRAL-2

	SOF/GS-5816 12 Weeks (N=134)	SOF+RBV 12 Weeks (N=132)
Number (%) of Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	2 (1.5%)	2 (1.5%)
Number (%) of Subjects Experiencing Any Treatment-Emergent Serious Adverse Event by Preferred Term		
Abdominal pain	1 (0.7%)	0
Arthralgia	0	1 (0.8%)
Depression	0	1 (0.8%)
Enteritis	1 (0.7%)	0
Pneumonia	1 (0.7%)	0

Table S6. Serious adverse events in ASTRAL-3

	SOF/GS-5816 12 Weeks (N=277)	SOF+RBV 24 Weeks (N=275)
Number (%) of Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	6 (2.2%)	15 (5.5%)
Number (%) of Subjects Experiencing Any Treatment-Emergent Serious Adverse Event by Preferred Term		
Acute myocardial infarction	1 (0.4%)	0
Bursitis	0	1 (0.4%)
Cellulitis	0	1 (0.4%)
Cerebrovascular accident	0	1 (0.4%)
Cholecystitis acute	1 (0.4%)	0
Chronic obstructive pulmonary disease	0	1 (0.4%)
Death	0	1 (0.4%)
Depression	0	1 (0.4%)
Food poisoning	1 (0.4%)	0
Forearm fracture	0	1 (0.4%)
Gun shot wound	0	1 (0.4%)
Haematochezia	1 (0.4%)	0
Intentional overdose	0	1 (0.4%)
Intervertebral disc protrusion	0	1 (0.4%)
Intracranial aneurysm	1 (0.4%)	0
Lung infection	0	1 (0.4%)
Ovarian cyst ruptured	1 (0.4%)	0
Peripheral artery stenosis	0	1 (0.4%)
Propionibacterium infection	0	1 (0.4%)
Psychotic disorder	0	1 (0.4%)
Rash maculo-papular	0	1 (0.4%)
Ruptured cerebral aneurysm	0	1 (0.4%)