Supplementary Appendix

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

Supplement to: Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. DOI: 10.1056/NEJMoa1402454

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Statistical Hypothesis for the Primary Efficacy Endpoint

The 4 primary statistical hypotheses of the study were that the SVR12 rates in each of the 4 treatment groups of the study would be higher than the adjusted historical SVR null rate of 60%.

This 60% SVR null rate is derived from:

1) A historical SVR rate of approximately 65% calculated from the telaprevir (ADVANCE study) and boceprevir (SPRINT2 study) data after adjusting for the expected proportion of subjects with cirrhosis (approximately 20%) in this study; and

2) a 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter duration of treatment. The weighted average of the telaprevir and boceprevir data is estimated to be approximately 70% in non-cirrhotic subjects, and 44% in cirrhotic subjects. The SVR rate for the historical control in this study (i.e., a patient population of 80% non-cirrhotics and 20% cirrhotics) is then calculated to be approximately 65% (i.e., 0.8 × 70% + 0.2 ×44%). As noted above, the 60% null SVR rate is obtained after allowing for a 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter treatment duration.

Calculation of Conditional Power for Interim Futility Analysis

To assess for futility in the two 12 week regimens, an interim futility stopping procedure used a conditional power approach under the observed trend. Stopping for futility would have been triggered when the conditional power was less than 5% (which was equivalent to an observed response rate of 60% or less). This assessment occurred when 50 subjects were evaluated for SVR4 in each 12-week treatment group. At the time of the assessment, we assumed that the SVR4 rates were equivalent to the SVR12 rates. The conditional power to reject the null hypothesis was calculated for the 12 week regimens, which is defined as the probability of rejecting the null hypothesis with 1-sided alpha level 0.025 at the final analysis conditional on the observed data at the interim analysis and assuming the future data would follow the observed trend. For each treatment group, let N = 200 be the sample size at the final analysis and M=50 be the sample size at the interim analysis. If the number of subjects achieving SVR4 was K at interim analysis, then the conditional power was,

$$\text{Conditional Power} = \text{Prob}\left(\left(\sum_{y=K+X}^{N} \binom{N}{y} p_0^y (1-p_0)^{N-y}\right) < 0.025 \,\middle|\, \text{Interim SVR4 rate} = \text{K out of M} \right)$$

$$= \sum_{A=0}^{N-M} \{ Index\left[\left(\sum_{y=K+A}^{N} \binom{N}{y} p_0^y (1-p_0)^{N-y}\right) < 0.025 \right] * \text{Prob}\left(X = A \,\middle|\, \text{Interim SVR4 rate} = \text{K out of M}\right) \}$$

where the first part is an index function, A was an integer between 0 and N-M, and X was a random variable representing the number of subjects achieved SVR12 at final analysis (out of N-M subjects enrolled in Part B for this treatment group). We assumed that X follows a binomial distribution Binomial(N-M, p=K/M) and for a given A between 0 and N-M, the probability of X equal to A was

$$P(X = A \mid p = \frac{K}{M}) = \binom{N-M}{A} (\frac{K}{M})^A (\frac{M-K}{M})^{N-M-A}$$

It was expected that approximately 50 subjects would have follow-up 4 weeks posttreatment in each of the two 12 Week regimens. Several possible futility criteria are listed in the table below with different numbers of subjects. The number in the first column represents the maximum number of subjects achieving SVR4 at interim that will meet the futility criteria (ie, the conditional power < 5%).

# SVR4	M *	SVR4 Rate	Conditional Power
≤ 30	49	≤ 61.2%	≤ 3.1%
≤ 30	50	≤ 60.0%	≤ 1.1%
≤ 31	51	≤ 60.8%	≤ 2.1%
≤ 32	52	≤ 61.5%	≤ 3.8%
≤ 32	53	≤ 60.4%	≤ 1.5%
≤ 33	54	≤ 61.1%	≤ 2.6%
≤ 34	55	≤ 61.8%	≤ 4.4%

* M: sample size at the interim analysis.

Table S1. Reasons for Screen Failure

Of the 1015 patients screened, 145 were screen failures.

Number patients who did not meet criteria	Inclusion criteria
55	Lab parameters at screening: ALT ≤10 × ULN, AST ≤10 × ULN, Hgb ≥12 g/dL (M) & 11 g/dL (F), Platelets ≥50,000/uL, INR ≤1.5, Albumin ≥3 g/dL, Direct bilirubin ≤1.5 × ULN, HbA1c ≤8.5%, Creatinine clearance ≥60 mL /min, INR ≤1.5 × ULN
14	HCV RNA ≥10^4 IU/mL at Screening
12	HCV genotype 1a, 1b, or mixed 1a/1b at Screening as determined by the Central Laboratory.
3	Screening ECG without clinically significant abnormalities
3	Subject must be able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.
3	Liver imaging within 6 months of Baseline/Day 1 to exclude hepatocellular carcinoma (HCC) is required in patients with cirrhosis
2	Subject must be of generally good health, with the exception of chronic HCV infection
2	Cirrhosis determination: a) Cirrhosis is defined as any one of the following: i) Liver biopsy showing cirrhosis (e.g., Metavir score = 4 or Ishak score ≥ 5), ii) FibroTest® score of > 0.75 AND an AST: platelet ratio index (APRI) of > 2 during Screening b) Absence of cirrhosis is defined as any one of the following: i) Liver biopsy within 2 years of Screening showing absence of cirrhosis, ii) FibroTest® score of ≤ 0.48 AND APRI of ≤ 1 during Screening c) In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy is required; liver biopsy results will supersede blood test results and be considered definitive.
1	Subject agrees to use of birth control
1	Willing and able to provide written informed consent
1	HCV treatment-naïve
	Exclusion criteria
15	Clinically relevant drug abuse within 12 months of screening.
7	History of clinically-significant illness or any other major medical disorder that may interfere with treatment, assessment, or compliance with the protocol
5	Prohibited concomitant medication
3	Alcohol misuse as defined by a Alcohol Use Disorders Identification Test (AUDIT) score ≥ 8
2	Pregnant or nursing female or male with pregnant female partner.
1	Infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV).
Number patients who did meet criteria	**Reason for non-enrollment**
14	Withdrew consent
7	Other
4	Lost to follow-up
1	Investigator's discretion

Figure S1. Patient Disposition

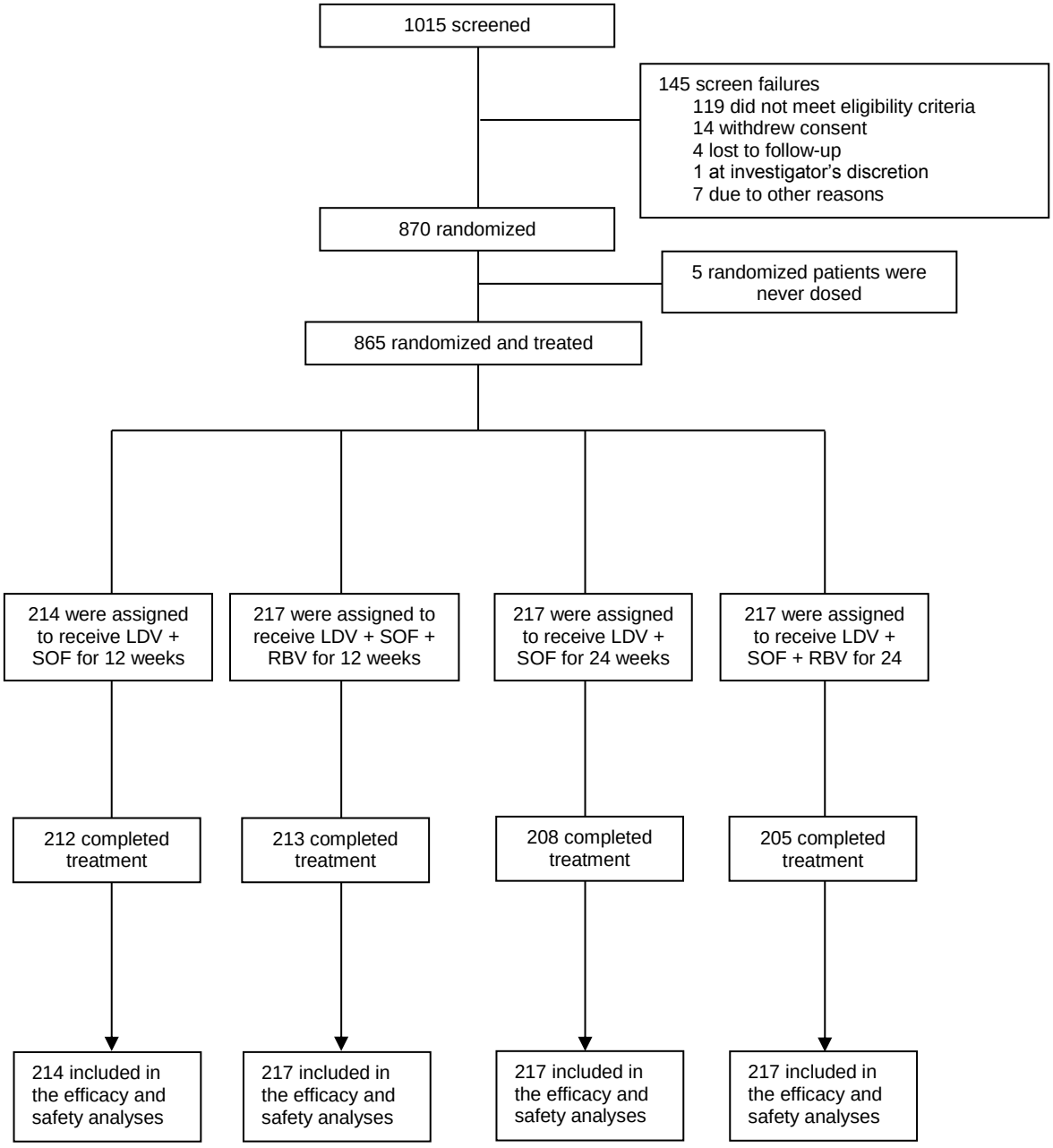

Figure S2. Sustained Virologic Response by Patient Characteristics, Intention to Treat analysis

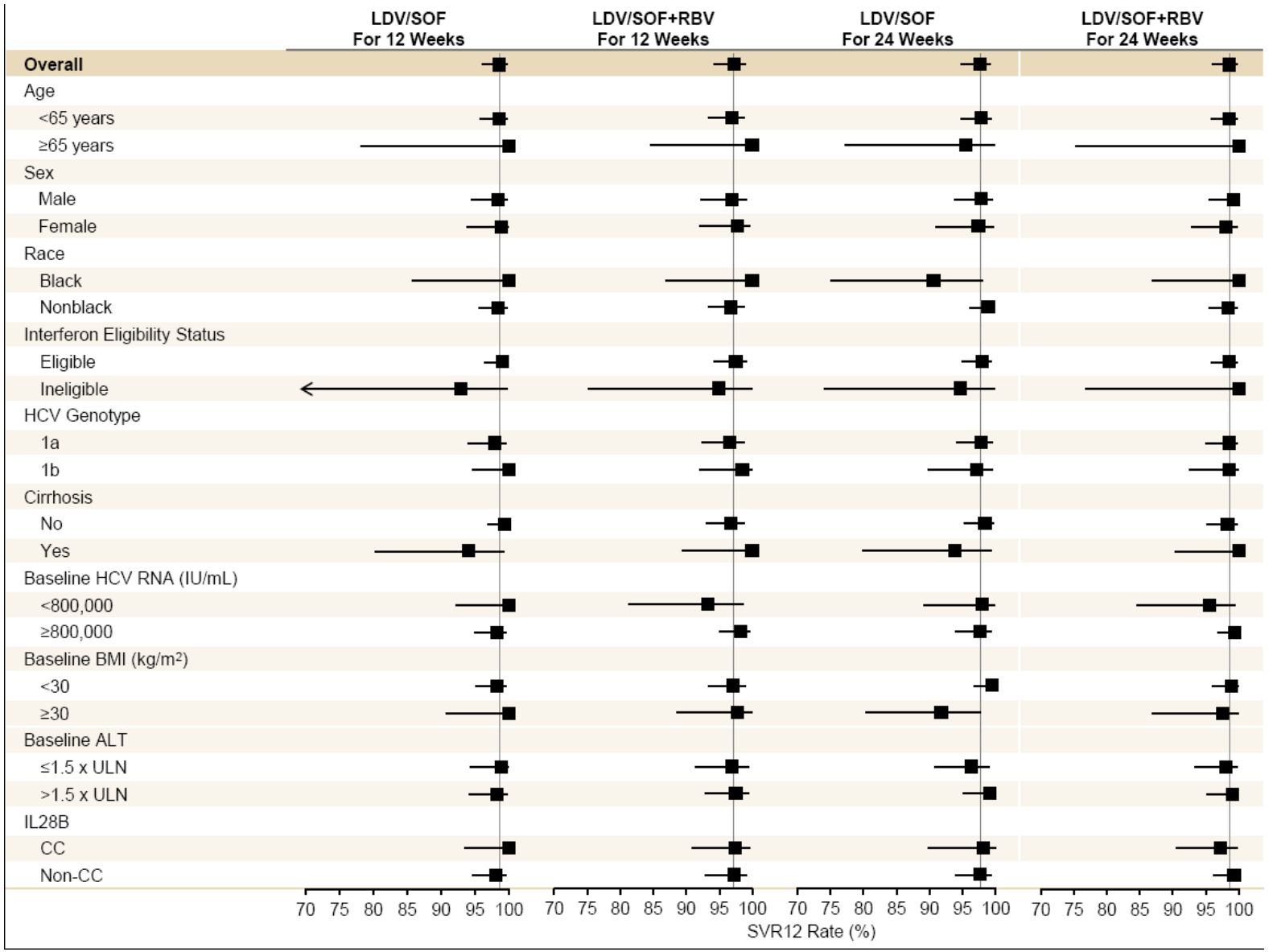

Table S2. Sustained Virologic Response by Subgroups

NOTE: subgroup results do not include patients who withdrew consent or were lost to follow-up.

	SOF/LDV 12 Weeks (N=214)	SOF/LDV+RBV 12 Weeks (N=217)	SOF/LDV 24 Weeks (N=217)	SOF/LDV+RBV 24 Weeks (N=217)
Overall	211/212 (99.5%)	211/211 (100.0%)	212/214 (99.1%)	215/215 (100.0%)
95% CI	97.4% to 100.0%	98.3% to 100.0%	96.7% to 99.9%	98.3% to 100.0%
Age at Baseline (Years)				
< 65	196/197 (99.5%)	189/189 (100.0%)	191/192 (99.5%)	202/202 (100.0%)
95% CI	97.2% to 100.0%	98.1% to 100.0%	97.1% to 100.0%	98.2% to 100.0%
>= 65	15/15 (100.0%)	22/22 (100.0%)	21/22 (95.5%)	13/13 (100.0%)
95% CI	78.2% to 100.0%	84.6% to 100.0%	77.2% to 99.9%	75.3% to 100.0%
Sex at Birth				
Male	125/126 (99.2%)	124/124 (100.0%)	136/138 (98.6%)	118/118 (100.0%)
95% CI	95.7% to 100.0%	97.1% to 100.0%	94.9% to 99.8%	96.9% to 100.0%
Female	86/86 (100.0%)	87/87 (100.0%)	76/76 (100.0%)	97/97 (100.0%)
95% CI	95.8% to 100.0%	95.8% to 100.0%	95.3% to 100.0%	96.3% to 100.0%
Race				
Black	24/24 (100.0%)	26/26 (100.0%)	29/31 (93.5%)	26/26 (100.0%)
95% CI	85.8% to 100.0%	86.8% to 100.0%	78.6% to 99.2%	86.8% to 100.0%
Non-Black	187/188 (99.5%)	184/184 (100.0%)	183/183 (100.0%)	188/188 (100.0%)
95% CI	97.1% to 100.0%	98.0% to 100.0%	98.0% to 100.0%	98.1% to 100.0%
Ethnicity				
Hispanic or Latino	26/26 (100.0%)	19/19 (100.0%)	29/29 (100.0%)	26/26 (100.0%)
95% CI	86.8% to 100.0%	82.4% to 100.0%	88.1% to 100.0%	86.8% to 100.0%
Not Hispanic or Latino	184/185 (99.5%)	192/192 (100.0%)	183/185 (98.9%)	188/188 (100.0%)
95% CI	97.0% to 100.0%	98.1% to 100.0%	96.1% to 99.9%	98.1% to 100.0%
Interferon Eligibility Status				
Eligible	198/199 (99.5%)	192/192 (100.0%)	194/196 (99.0%)	201/201 (100.0%)
95% CI	97.2% to 100.0%	98.1% to 100.0%	96.4% to 99.9%	98.2% to 100.0%
Ineligible	13/13 (100.0%)	19/19 (100.0%)	18/18 (100.0%)	14/14 (100.0%)
95% CI	75.3% to 100.0%	82.4% to 100.0%	81.5% to 100.0%	76.8% to 100.0%
HCV Genotype				
1a	141/142 (99.3%)	143/143 (100.0%)	143/143 (100.0%)	141/141 (100.0%)
95% CI	96.1% to 100.0%	97.5% to 100.0%	97.5% to 100.0%	97.4% to 100.0%
1b	66/66 (100.0%)	67/67 (100.0%)	66/68 (97.1%)	71/71 (100.0%)
95% CI	94.6% to 100.0%	94.6% to 100.0%	89.8% to 99.6%	94.9% to 100.0%
Other	4/4 (100.0%)	1/1 (100.0%)	3/3 (100.0%)	3/3 (100.0%)
95% CI	39.8% to 100.0%	2.5% to 100.0%	29.2% to 100.0%	29.2% to 100.0%
Cirrhosis				
No	179/179 (100.0%)	178/178 (100.0%)	181/182 (99.5%)	179/179 (100.0%)
95% CI	98.0% to 100.0%	97.9% to 100.0%	97.0% to 100.0%	98.0% to 100.0%
Yes	32/33 (97.0%)	33/33 (100.0%)	31/32 (96.9%)	36/36 (100.0%)
95% CI	84.2% to 99.9%	89.4% to 100.0%	83.8% to 99.9%	90.3% to 100.0%
Baseline HCV RNA (IU/mL)				
< 800,000	45/45 (100.0%)	41/41 (100.0%)	48/48 (100.0%)	43/43 (100.0%)
95% CI	92.1% to 100.0%	91.4% to 100.0%	92.6% to 100.0%	91.8% to 100.0%
>= 800,000	166/167 (99.4%)	170/170 (100.0%)	164/166 (98.8%)	172/172 (100.0%)
95% CI	96.7% to 100.0%	97.9% to 100.0%	95.7% to 99.9%	97.9% to 100.0%

Table S2. Sustained Virologic Response by Subgroups (continued)

	SOF/LDV 12 Weeks (N=214)	SOF/LDV+RBV 12 Weeks (N=217)	SOF/LDV 24 Weeks (N=217)	SOF/LDV+RBV 24 Weeks (N=217)
Baseline Body Mass Index (kg/m2)				
< 30	173/174 (99.4%)	166/166 (100.0%)	167/167 (100.0%)	176/176 (100.0%)
95% CI	96.8% to 100.0%	97.8% to 100.0%	97.8% to 100.0%	97.9% to 100.0%
>= 30	38/38 (100.0%)	45/45 (100.0%)	45/47 (95.7%)	39/39 (100.0%)
95% CI	90.7% to 100.0%	92.1% to 100.0%	85.5% to 99.5%	91.0% to 100.0%
Baseline ALT				
<= 1.5 x ULN	93/93 (100.0%)	95/95 (100.0%)	104/106 (98.1%)	104/104 (100.0%)
95% CI	96.1% to 100.0%	96.2% to 100.0%	93.4% to 99.8%	96.5% to 100.0%
> 1.5 x ULN	118/119 (99.2%)	116/116 (100.0%)	108/108 (100.0%)	111/111 (100.0%)
95% CI	95.4% to 100.0%	96.9% to 100.0%	96.6% to 100.0%	96.7% to 100.0%
Region				
US	122/123 (99.2%)	115/115 (100.0%)	129/131 (98.5%)	136/136 (100.0%)
95% CI	95.6% to 100.0%	96.8% to 100.0%	94.6% to 99.8%	97.3% to 100.0%
Europe	89/89 (100.0%)	96/96 (100.0%)	83/83 (100.0%)	79/79 (100.0%)
95% CI	95.9% to 100.0%	96.2% to 100.0%	95.7% to 100.0%	95.4% to 100.0%
IL28B				
CC	55/55 (100.0%)	74/74 (100.0%)	51/51 (100.0%)	71/71 (100.0%)
95% CI	93.5% to 100.0%	95.1% to 100.0%	93.0% to 100.0%	94.9% to 100.0%
Non-CC	156/157 (99.4%)	137/137 (100.0%)	161/163 (98.8%)	144/144 (100.0%)
95% CI	96.5% to 100.0%	97.3% to 100.0%	95.6% to 99.9%	97.5% to 100.0%
CT	111/111 (100.0%)	103/103 (100.0%)	118/119 (99.2%)	112/112 (100.0%)
95% CI	96.7% to 100.0%	96.5% to 100.0%	95.4% to 100.0%	96.8% to 100.0%
TT	45/46 (97.8%)	34/34 (100.0%)	43/44 (97.7%)	32/32 (100.0%)
95% CI	88.5% to 99.9%	89.7% to 100.0%	88.0% to 99.9%	89.1% to 100.0%
Baseline Albumin (g/dL)				
< 3.5	5/6 (83.3%)	6/6 (100.0%)	11/11 (100.0%)	12/12 (100.0%)
95% CI	35.9% to 99.6%	54.1% to 100.0%	71.5% to 100.0%	73.5% to 100.0%
>= 3.5	206/208 (99.0%)	205/211 (97.2%)	201/206 (97.6%)	203/205 (99.0%)
95% CI	96.6% to 99.9%	93.9% to 98.9%	94.4% to 99.2%	96.5% to 99.9%
Baseline Platelets (x10^3/uL)				
< 90	4/5 (80.0%)	6/6 (100.0%)	8/8 (100.0%)	4/4 (100.0%)
95% CI	28.4% to 99.5%	54.1% to 100.0%	63.1% to 100.0%	39.8% to 100.0%
>= 90	207/209 (99.0%)	205/211 (97.2%)	204/209 (97.6%)	211/213 (99.1%)
95% CI	96.6% to 99.9%	93.9% to 98.9%	94.5% to 99.2%	96.6% to 99.9%
Baseline Albumin (g/dL) < 3.5				
Baseline Platelets (x10^3/uL) < 90	0/1	3/3 (100.0%)	3/3 (100.0%)	0/0
95% CI	0.0% to 97.5%	29.2% to 100.0%	29.2% to 100.0%	
Baseline Platelets (x10^3/uL) >= 90	5/5 (100.0%)	3/3 (100.0%)	8/8 (100.0%)	12/12 (100.0%)
95% CI	47.8% to 100.0%	29.2% to 100.0%	63.1% to 100.0%	73.5% to 100.0%
Baseline Albumin (g/dL) >= 3.5				
Baseline Platelets (x10^3/uL) < 90	4/4 (100.0%)	3/3 (100.0%)	5/5 (100.0%)	4/4 (100.0%)
95% CI	39.8% to 100.0%	29.2% to 100.0%	47.8% to 100.0%	39.8% to 100.0%
Baseline Platelets (x10^3/uL) >= 90	202/204 (99.0%)	202/208 (97.1%)	196/201 (97.5%)	199/201 (99.0%)
95% CI	96.5% to 99.9%	93.8% to 98.9%	94.3% to 99.2%	96.5% to 99.9%

Table S3. Proportion of Subjects with HCV RNA <25 IU/mL While on Treatment

	SOF/LDV 12 Weeks (N=214)	SOF/LDV+RBV 12 Weeks (N=217)	SOF/LDV 24 Weeks (N=217)	SOF/LDV+RBV 24 Weeks (N=217)
Baseline				
< LLOQ	0/214	0/217	0/217	0/217
Week 1				
< LLOQ	83/213 (39.0%)	65/217 (30.0%)	70/217 (32.3%)	71/217 (32.7%)
95% CI	32.4% to 45.9%	23.9% to 36.5%	26.1% to 38.9%	26.5% to 39.4%
< LLOQ detected	76/213 (35.7%)	59/217 (27.2%)	59/217 (27.2%)	63/217 (29.0%)
< LLOQ TND	7/213 (3.3%)	6/217 (2.8%)	11/217 (5.1%)	8/217 (3.7%)
Week 2				
< LLOQ	174/213 (81.7%)	181/217 (83.4%)	179/216 (82.9%)	180/217 (82.9%)
95% CI	75.8% to 86.6%	77.8% to 88.1%	77.2% to 87.6%	77.3% to 87.7%
< LLOQ detected	103/213 (48.4%)	111/217 (51.2%)	113/216 (52.3%)	113/217 (52.1%)
< LLOQ TND	71/213 (33.3%)	70/217 (32.3%)	66/216 (30.6%)	67/217 (30.9%)
Week 4				
< LLOQ	213/213 (100.0%)	215/217 (99.1%)	216/216 (100.0%)	217/217 (100.0%)
95% CI	98.3% to 100.0%	96.7% to 99.9%	98.3% to 100.0%	98.3% to 100.0%
< LLOQ detected	44/213 (20.7%)	36/217 (16.6%)	37/216 (17.1%)	46/217 (21.2%)
< LLOQ TND	169/213 (79.3%)	179/217 (82.5%)	179/216 (82.9%)	171/217 (78.8%)
Week 6				
< LLOQ	213/213 (100.0%)	216/216 (100.0%)	216/216 (100.0%)	217/217 (100.0%)
95% CI	98.3% to 100.0%	98.3% to 100.0%	98.3% to 100.0%	98.3% to 100.0%
< LLOQ detected	7/213 (3.3%)	4/216 (1.9%)	5/216 (2.3%)	4/217 (1.8%)
< LLOQ TND	206/213 (96.7%)	212/216 (98.1%)	211/216 (97.7%)	213/217 (98.2%)
Week 8				
< LLOQ	212/213 (99.5%)	215/215 (100.0%)	215/216 (99.5%)	217/217 (100.0%)
95% CI	97.4% to 100.0%	98.3% to 100.0%	97.4% to 100.0%	98.3% to 100.0%
< LLOQ detected	3/213 (1.4%)	0/215	2/216 (0.9%)	0/217
< LLOQ TND	209/213 (98.1%)	215/215 (100.0%)	213/216 (98.6%)	217/217 (100.0%)
Week 10				
< LLOQ	213/213 (100.0%)	215/215 (100.0%)	214/215 (99.5%)	216/216 (100.0%)
95% CI	98.3% to 100.0%	98.3% to 100.0%	97.4% to 100.0%	98.3% to 100.0%
< LLOQ detected	1/213 (0.5%)	0/215	0/215	1/216 (0.5%)
< LLOQ TND	212/213 (99.5%)	215/215 (100.0%)	214/215 (99.5%)	215/216 (99.5%)
Week 12				
< LLOQ	213/213 (100.0%)	214/214 (100.0%)	213/214 (99.5%)	216/216 (100.0%)
95% CI	98.3% to 100.0%	98.3% to 100.0%	97.4% to 100.0%	98.3% to 100.0%
< LLOQ detected	1/213 (0.5%)	1/214 (0.5%)	1/214 (0.5%)	0/216
< LLOQ TND	212/213 (99.5%)	213/214 (99.5%)	212/214 (99.1%)	216/216 (100.0%)
Week 16				
< LLOQ	N/A	N/A	211/211 (100.0%)	214/214 (100.0%)
95% CI	N/A	N/A	98.3% to 100.0%	98.3% to 100.0%
< LLOQ detected	N/A	N/A	0/211	1/214 (0.5%)
< LLOQ TND	N/A	N/A	211/211 (100.0%)	213/214 (99.5%)
Week 20				
< LLOQ	N/A	N/A	210/210 (100.0%)	209/209 (100.0%)
95% CI	N/A	N/A	98.3% to 100.0%	98.3% to 100.0%
< LLOQ detected	N/A	N/A	0/210	1/209 (0.5%)
< LLOQ TND	N/A	N/A	210/210 (100.0%)	208/209 (99.5%)
Week 24				
< LLOQ	N/A	N/A	209/209 (100.0%)	207/207 (100.0%)
95% CI	N/A	N/A	98.3% to 100.0%	98.2% to 100.0%
< LLOQ detected	N/A	N/A	0/209	0/207
< LLOQ TND	N/A	N/A	209/209 (100.0%)	207/207 (100.0%)

Table S4. Phenotypic Analysis of NS5A and NS5B Isolates for Patients Who Relapsed

Subject ID	GT	Treatment	Relevant RAVs				Drug Susceptibility (Fold-Change from Reference)					
			NS5A		NS5B[a]		LDV[b]		SOF[c]		RBV[c]	
			BL	RAVs at Post BL	BL	RAVs at Post BL	BL	Post BL	BL	Post BL	BL	Post BL
1603-71276[d]	1a	12 Weeks SOF/LDV	L31M (> 99%)	L31M (> 99%)	None	None	> 42	> 42	0.84	0.9	0.79	0.99
5663-71589[e]	1b	24 Weeks SOF/LDV	None	Y93H (> 99%)	None	None	0.67	> 208	0.88	0.72	1.1	0.79

BL = baseline; GT = genotype

a NS5B NI RAVs were defined as the following substitutions at positions: S96T, N142T, L159F, S282T, M289L, L320F, and V321A. RBV RAVs were defined as the following substitutions at positions: F415Y and T390I.

b Fold-Change from reference as tested in a NS5A Replicon System

c Fold-Change from reference as tested in a NS5B Replicon System

d Postbaseline timepoint is posttreatment Week 4

e Postbaseline timepoint is Week 8 of treatment

Table S5. Serious Adverse Events

	SOF/LDV 12 Weeks (N=214)	SOF/LDV+RBV 12 Weeks (N=217)	SOF/LDV 24 Weeks (N=217)	SOF/LDV+RBV 24 Weeks (N=217)
Number (%) of Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	1 (0.5%)	7 (3.2%)	18 (8.3%)	7 (3.2%)
Number (%) of Subjects Experiencing Any Treatment-Emergent Serious Adverse Event by Preferred Term				
CELLULITIS	0	0	1 (0.5%)	1 (0.5%)
CHEST PAIN	1 (0.5%)	0	1 (0.5%)	0
GASTROENTERITIS	0	0	2 (0.9%)	0
HAND FRACTURE	0	0	2 (0.9%)	0
NON-CARDIAC CHEST PAIN	0	1 (0.5%)	1 (0.5%)	0
PNEUMONIA	0	1 (0.5%)	0	1 (0.5%)
ABDOMINAL DISCOMFORT	0	0	1 (0.5%)	0
ABDOMINAL PAIN UPPER	0	0	1 (0.5%)	0
ALCOHOL POISONING	0	0	0	1 (0.5%)
ALCOHOL WITHDRAWAL SYNDROME	0	0	0	1 (0.5%)
ANAEMIA	0	1 (0.5%)	0	0
BREAST MASS	0	0	1 (0.5%)	0
CALCULUS URETERIC	0	0	0	1 (0.5%)
CAROTID ARTERY STENOSIS	0	0	0	1 (0.5%)
COLITIS	0	0	1 (0.5%)	0
CONCUSSION	0	0	0	1 (0.5%)
DEPRESSION	0	0	0	1 (0.5%)
FACTOR VIII INHIBITION	0	0	1 (0.5%)	0
FALL	0	0	1 (0.5%)	0
FOOT FRACTURE	0	0	1 (0.5%)	0
HEADACHE	0	0	1 (0.5%)	0
HYPERTENSION	0	1 (0.5%)	0	0
INTERVERTEBRAL DISC PROTRUSION	0	1 (0.5%)	0	0
LOWER LIMB FRACTURE	0	0	1 (0.5%)	0

Table S6. Adverse Events Leading to Permanent Discontinuation from Ledipasvir-Sofosbuvir

	SOF/LDV 12 Weeks (N=214)	SOF/LDV+RBV 12 Weeks (N=217)	SOF/LDV 24 Weeks (N=217)	SOF/LDV+RBV 24 Weeks (N=217)
Number (%) of Subjects Experiencing Any Adverse Event Leading to Permanent Discontinuation from SOF/LDV	0	0	4 (1.8%)	6 (2.8%)
Number (%) of Subjects Experiencing Any Adverse Event Leading to Permanent Discontinuation from SOF/LDV by Preferred Term				
ANXIETY	0	0	0	2 (0.9%)
PALPITATIONS	0	0	1 (0.5%)	1 (0.5%)
CHEST PAIN	0	0	1 (0.5%)	0
DIZZINESS	0	0	1 (0.5%)	0
DYSPNOEA	0	0	0	1 (0.5%)
EAR PAIN	0	0	0	1 (0.5%)
EYELID OEDEMA	0	0	0	1 (0.5%)
FACTOR VIII INHIBITION	0	0	1 (0.5%)	0
FATIGUE	0	0	0	1 (0.5%)
GASTROINTESTINAL VIRAL INFECTION	0	0	0	1 (0.5%)
HAEMORRHAGE	0	0	1 (0.5%)	0
HEADACHE	0	0	0	1 (0.5%)
SENSORY DISTURBANCE	0	0	0	1 (0.5%)
THROAT TIGHTNESS	0	0	1 (0.5%)	0
VERTIGO	0	0	0	1 (0.5%)