Supplementary information

Determination of minimum historical target SVR12 rate (PegIFN-ineligible patients)

Determining the minimum acceptable SVR rate for PegIFN-ineligible patients was challenging since there are no approved regimens for this population in which to benchmark. It was assumed that this population would be more difficult to treat than the typical PegIFN-eligible population due to more co-morbidities leading to more discontinuations and potential non-compliance. Although more co-morbidities may have led to increased AE reporting (eg exaggeration of an underlying baseline condition), non-compliance would have led to higher breakthrough rates. These issues could have negatively affected the SVR rates. Before enrolling patients in the trial, and without a cap of this PegIFN-ineligible population, the proportion of such patients within the overall study population of 1241.36 was unclear. Therefore, investigators were asked to flag whether a patient was deemed PegIFN-eligible or not at randomization, which was stratified for this important factor.

Table S1 presents the primary reasons patients fail treatment with a DAA-based regimen, including early discontinuations due to AEs, on-treatment virologic failure (OT VF) and relapse. A 71% SVR rate (benchmark for the PegIFN-eligible population without 5% reduction) was categorized by 10% rates of each type of failure (early discontinuation, OT VF, and relapse). These were roughly the different categories for failure observed in SOUND-C2. These patients were not expected to have greater relapse rates, so assumptions about increase rates in reasons for failure were restricted to early discontinuations and OT VF rates. A minor increase in one of these factors combined with a major increase in the occurrence of the other, or moderate increases in both, would result in SVR rates of 50% compared to the base case of 71%.

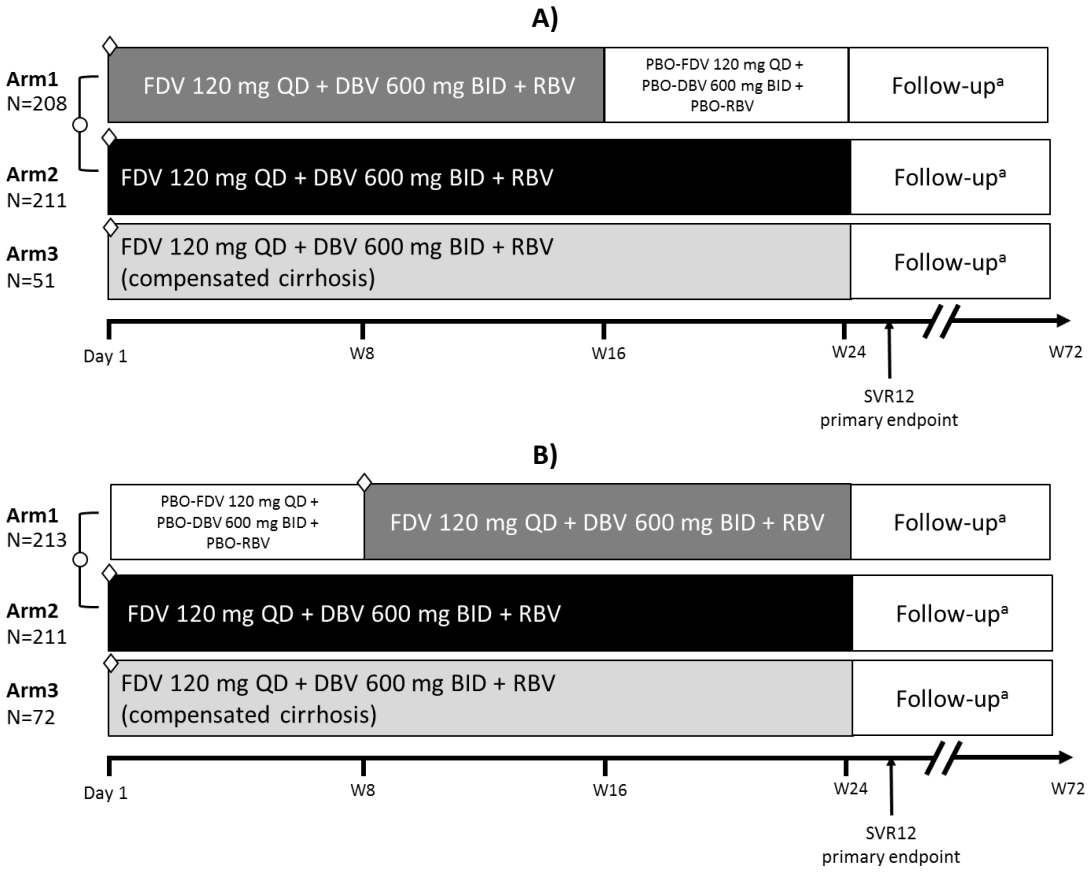
This rationale was based on many assumptions, but these patients had no alternative options for treatment, unlike PegIFN-eligible patients. Thus, any regimen that achieved 50% SVR was desirable and, prior to the recent approval of DAAS, such a response for GT1b-infected PegIFN-eligible patients had been the goal for many years.

Table S1. Summary of assumptions and results utilized in the calculation of 50% for determination of minimum SVR rated within PegIFN-ineligible patients.

DC %	OT VF %	Relapse %	SVR %	Comment
10	10	10	70	Base case (~minimum SVR for TN)
15	15	10	60	
15	20	10	55	
15	25	10	50	Minor increase in DC rate; large increase in OT VF rate (eg due to compliance issues)
20	15	10	55	
20	20	10	50	Moderate increases in both DC and OT VF rates
20	25	10	45	
25	15	10	50	Large increase in DC rate; minor increase in OT VF rate
25	20	10	45	
25	25	10	40	

DC, discontinuation; OT VF, on-treatment virologic failure.

Fig. S1. Study design for HCVerso1 (A) and HCVerso2 (B)

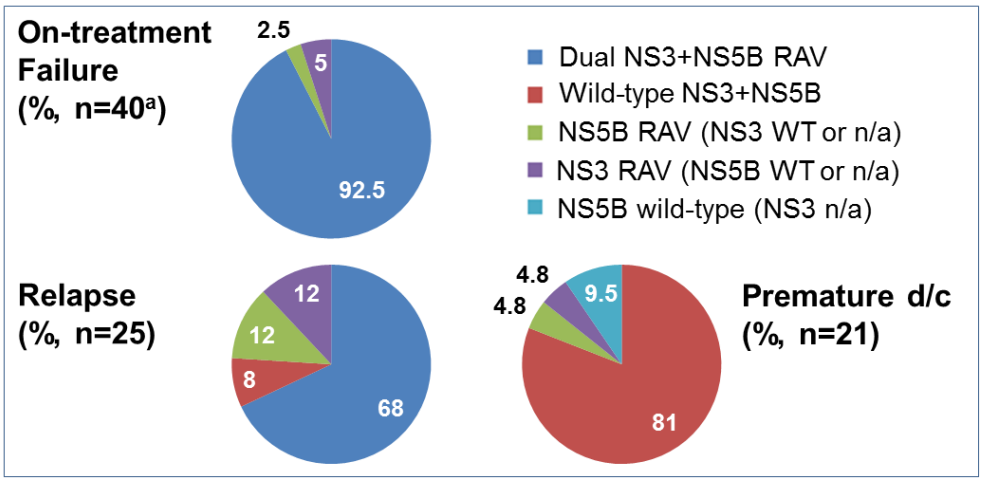


○ Randomization; ◊ loading dose of FDV 240 mg on Day 1; RBV was dosed BID at 1000 mg/day (body weight <75 kg), or 1200 mg/day (body weight ≥75 kg).

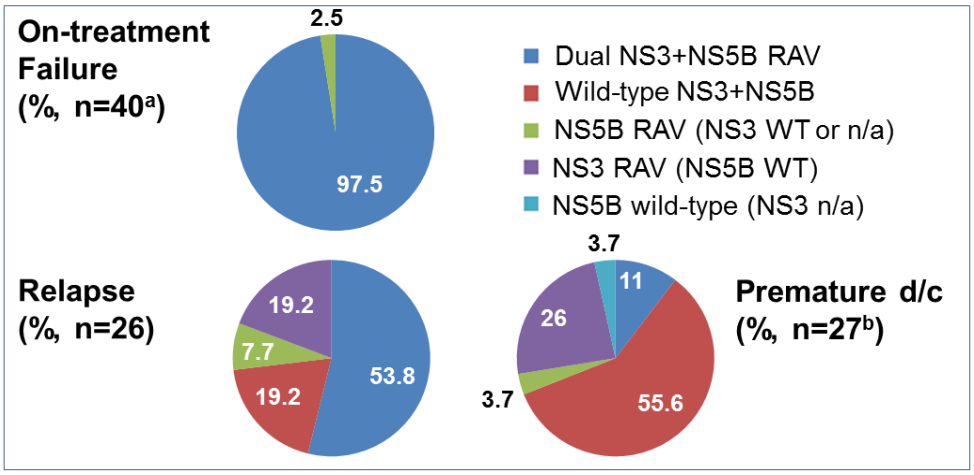
[a]Following termination of DBV development, the follow-up period was shortened from 96 weeks after end of treatment to 24 weeks after end of treatment for responders (for SVR12), and 48 weeks after end of treatment for non-responders. BID, twice daily; DBV, deleobuvir; FDV, faldaprevir; PBO, placebo; QD, once daily; RBV, ribavirin; SVR12, sustained virologic response 12 weeks post treatment; W, week.

Fig. S2. Frequency of resistance-associated variants in patients not achieving SVR12 in HCVerso1 (A) and HCVerso2 (B)

A)



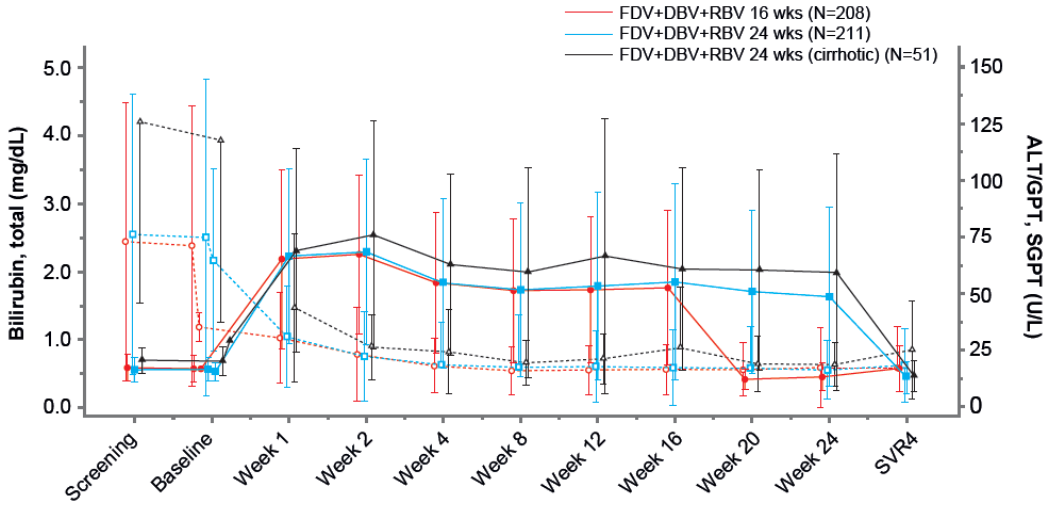
B)



Only non-SVR12 patients with available GT-1b baseline and post-baseline sequence are described. Analysis of the NS3 region included R155, A156, and D168 RAVs, and the NS5B region included A421, P495, P496, and V499 RAVs. [a]In both studies, on-treatment failure includes patients with virologic breakthrough and 2 patients with lack of end of treatment response. [b]Includes premature discontinuations and excludes 2 patients who discontinued during placebo. d/c, discontinuation; n/a, sequence not available; RAV, resistance-associated variants; WT, wild-type.

Figure S3. Total bilirubin (solid line) and ALT levels (dashed line) (mean ± SD) over time in HCVerso1 (A) and HCVerso2 (B)

A)



B)

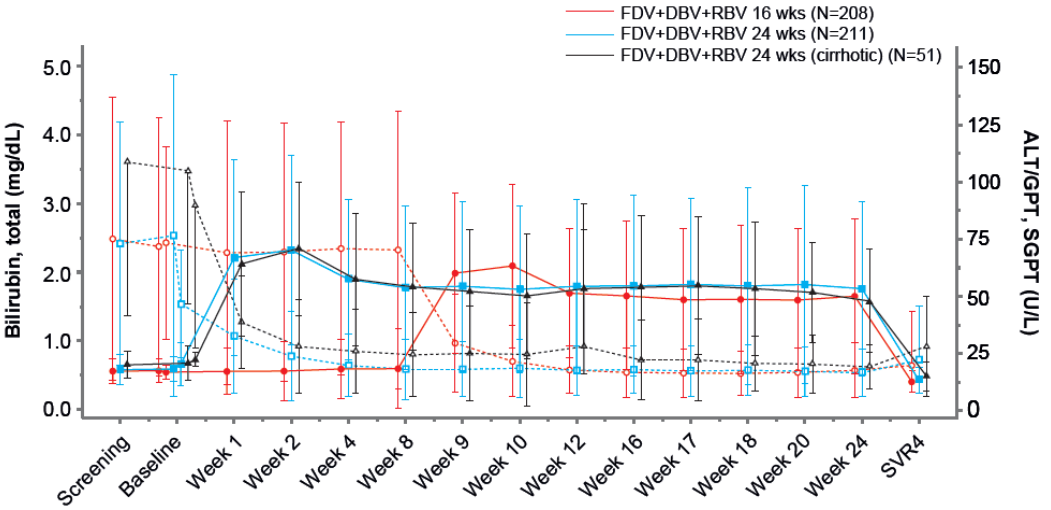


Table S2. Exclusion criteria related to PegIFN/RBV eligibility

	HCVerso1	HCVerso2
Pre-existing psychiatric conditions	Excluded	Not excluded
Abnormal thyroid function that cannot be controlled effectively by medication	Excluded	Not excluded
Active autoimmune-mediated disease	Excluded	Not excluded
Requirement for chronic systemic corticosteroids	Excluded	Not excluded
History or other evidence of severe retinopathy or clinically significant ophthalmological disorder due to diabetes mellitus or hypertension	Excluded	Not excluded
Hemoglobin	Exclude: <11.0 g/dL for women and <12.0 g/dL for men	Exclude: <11.0 g/dL for women and <12.0 g/dL for men
Absolute neutrophil count	Exclude: <1,500 cells/mm^3	Exclude: <1,000 cells/mm^3
Platelet count	Exclude: <90,000/mm^3	Exclude: <70,000mm^3
Creatinine clearance	Exclude: ≤50 mL/min	Not excluded
Diabetes mellitus	Exclude: HbA1c >8.5%	Not excluded
Clinically evident red blood cell disorders	Excluded	Excluded

Table S3. Association of baseline factors with SVR12 (multivariate logistic regression)

Study	**Baseline factor**	***P*-value**	**Odds ratio (95% CI)**
HCVerso1	Treatment	0.0226	
	24-week NC vs 16-week NC		2.079 (1.230, 3.513)
	24-week Cr vs 16-week NC		1.195 (0.552, 2.586)
	IL28B rs 12979860	0.0051	
	CC vs non-CC		2.538 (1.322, 4.873)
	Gender	0.0089	
	Male vs female		0.517 (0.315, 0.847)
	Region	0.0029	
	North America vs Europe		0.435 (0.252, 0.753)
HCVerso2	Treatment	0.0869	1.513 (0.894, 2.562)
	24-week NC vs 16-week NC		0.716 (0.362, 1.416)
	24-week Cr vs 16-week NC		
	IL28B rs 12979860	0.0108	
	CC vs non-CC		2.239 (1.205, 4.163)
	Baseline HCV RNA	0.0195	
	=800,000 vs <800,000		0.436 (0.217, 0.875)
	Gender	0.0071	
	Male vs female		0.514 (0.316, 0.835)

CI, confidence interval; Cr, cirrhotic; NC, non-cirrhotic.