Supplementary Appendix

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

Supplement to: Zeuzem S, Soriano V, Asselah T, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. N Engl J Med 2013;369:630-9. DOI: 10.1056/NEJMoa1213557

SUPPLEMENTARY APPENDIX

Additional Figures and Tables

for

Faldaprevir and Deleobuvir for HCV Genotype 1 Infection

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Table of Contents

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Figure S1. Patient Disposition

*Enrolment to the ribavirin-free arm was stopped at the request of the FDA, following the observation from other studies that breakthrough was more common in interferon-free regimens that did not contain ribavirin compared with those that did[18,21]

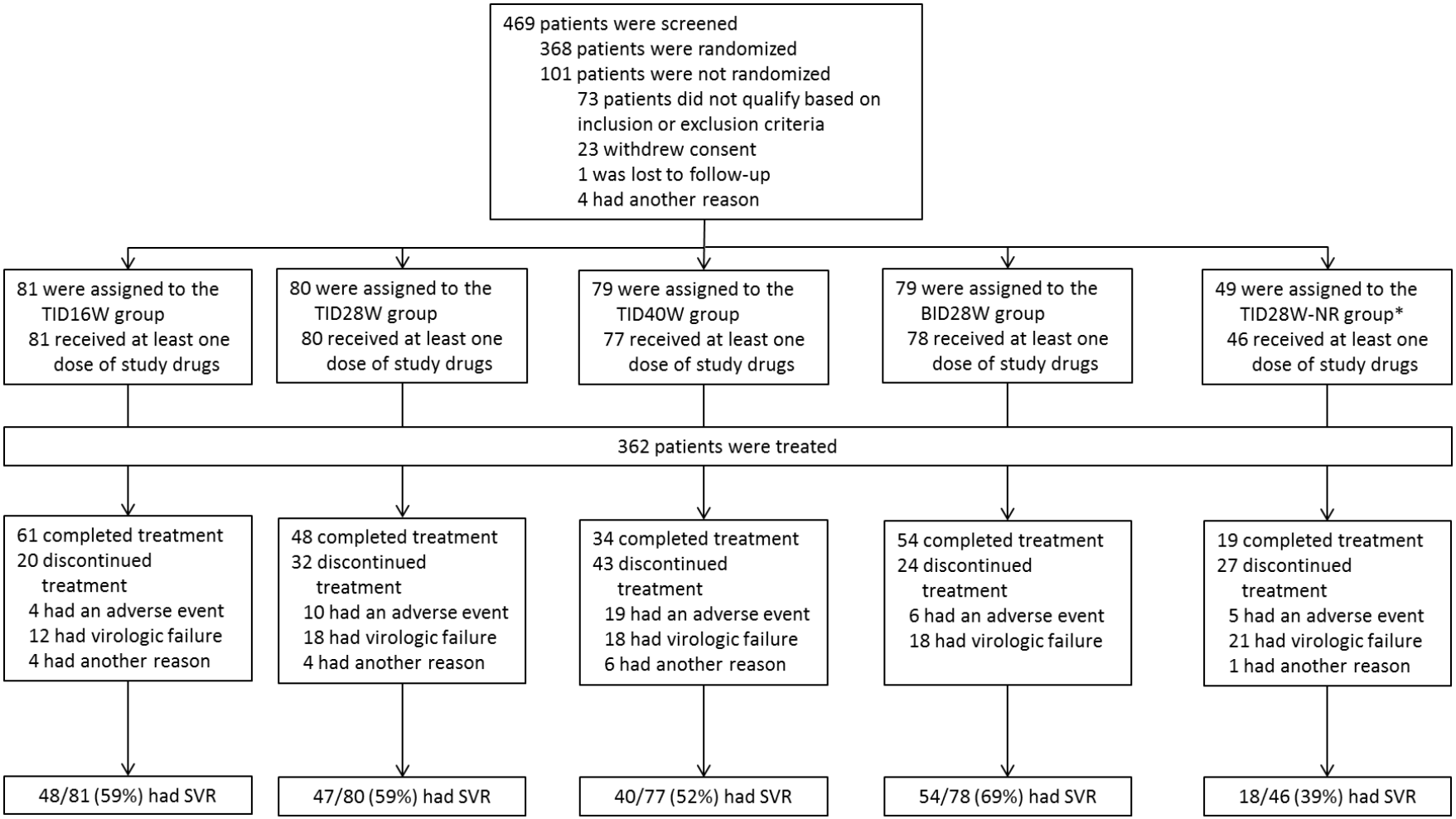

Table S1. Secondary efficacy endpoints

	TID16W (N=81)	TID28W (N=80)	TID40W (N=77)	BID28W (N=78)	TID28W-NR (N=46)
Undetectable HCV RNA week 4—no. (%)	53 (65)	48 (60)	49 (64)	44 (56)	23 (50)
Undetectable HCV RNA at end of treatment—no. (%)	64 (79)	57 (71)	51 (66)	55 (71)	21 (46)
Undetectable HCV RNA 24 weeks after the end of treatment—no. (%)	47 (58)	47 (59)	38 (49)	54 (69)	18 (39)

Table S2. Multivariate Logistic Regression Relationship between Baseline Factors and Sustained Virologic Response in a Per-Protocol Analysis

	Odds ratio (95% CI)	Chi-squared	P value
Subtype			
1b:1a	7.40 (3.98–13.77)	39.93	<0.001
IL28B			
CC:non-CC	5.20 (2.35–11.47)	16.63	<0.001
Sex			
Female:male	3.81 (2.06–7.03)	18.26	<0.001
Treatment Group			
TID16W:TID28W-NR	3.69 (1.33–10.27)	6.26	0.01
TID28W:TID28W-NR	4.29 (1.51–12.15)	7.50	0.006
TID40W:TID28W-NR	3.66 (1.24–10.77)	5.54	0.01
BID28W:TID28W-NR	5.06 (1.79–14.29)	9.38	0.002
Baseline GGT			
Normal:>ULN	2.15 (1.18–3.92)	6.23	0.013

The per-protocol analysis excludes patients who prematurely discontinued the planned treatment for reasons other than lack of efficacy or those with efficacy related important protocol violations (i.e. patients who were not virologically evaluable were excluded).

Table S3. Resistance Associated Variants that Emerged in Patients with Breakthrough or Relapse

	Mutation(s)	**Prevalence n/N (%)**
Genotype 1a		
Breakthrough	NS3 R155K + NS5B P495L/S/T	45/50 (90)
	NS3 D168V/Y + NS5B P495L	3/50 (6)
	Dual NS3 (R155T + D168N) + NS5B P495L	1/50 (2)
	Dual NS3 (R155K + D168V) + NS5B Wildtype	1/50 (2)
Relapse	NS3 R155K	7/11 (64)
	NS3 R155K + NS5B P495L/Q	4/11 (36)
Genotype 1b		
Breakthrough	NS3 D168V/Y + NS5B P495L/S/Q	16/25 (64)
	Dual NS3 (R155G + D168N) + NS5B P495L	4/25 (16)
	NS3 R155Q/K/W + NS5B P495L	4/25 (16)
	N/A. below limit of amplification (NS3 + NS5B)	1/25 (4)
Relapse	Single NS3 D168V	1/4 (25)
	Single NS5B P495L	1/4 (25)
	Wildtype at both loci	2/4 (50)

Table S4. Incidence of Serious Adverse Events According to Treatment Group

	TID16W (N=81)	TID28W (N=80)	TID40W (N=77)	BID28W (N=78)	TID28W-NR (N=46)
Serious adverse events—n (%)	**3 (4)**	**8 (10)**	**5 (6)**	**8 (10)**	**3 (7)**
Infections and infestations	**1 (1)**	**1 (1)**	**0**	**1 (1)**	**0**
Gastroenteritis	0	1 (1)	0	0	0
Herpes zoster	0	0	0	1 (1)	0
Cellulitis pharyngeal	1 (1)	0	0	0	0
Blood and lymphatic system disorders	**0**	**1 (1)**	**0**	**2 (3)**	**0**
Anaemia	0	1 (1)	0	1 (1)	0
Febrile neutropenia	0	0	0	1 (1)	0
Metabolism and nutrition disorders	**0**	**1 (1)**	**0**	**1 (1)**	**0**
Dehydration	0	1 (1)	0	1 (1)	0
Psychiatric disorders	**0**	**0**	**1 (1)**	**0**	**0**
Psychotic disorder	0	0	1 (1)	0	0
Nervous system disorders	**0**	**0**	**0**	**2 (3)**	**0**
Convulsion	0	0	0	1 (1)	0
Hypoxic−ischaemic encephalopathy	0	0	0	1 (1)	0
Syncope	0	0	0	1 (1)	0
Cardiac disorders	**0**	**1 (1)**	**0**	**1 (1)**	**0**
Bundle branch block left	0	1 (1)	0	0	0
Cardiac arrest	0	0	0	1 (1)	0
Cardiopulmonary failure	0	0	0	1 (1)	0
Coronary artery stenosis	0	0	0	1 (1)	0
Myocardial infarction	0	0	0	1 (1)	0

	TID16W (N=81)	TID28W (N=80)	TID40W (N=77)	BID28W (N=78)	TID28W-NR (N=46)
Ventricular fibrillation	0	0	0	1 (1)	0
Respiratory, thoracic and mediastinal disorders	**0**	**1 (1)**	**0**	**1 (1)**	**0**
Pulmonary embolism	0	1 (1)	0	0	0
Respiratory failure	0	0	0	1 (1)	0
Gastrointestinal disorders	**0**	**1 (1)**	**2 (3)**	**0**	**0**
Abdominal pain	0	1 (1)	0	0	0
Diarrhea	0	0	1 (1)	0	0
Haemorrhoids	0	0	1 (1)	0	0
Nausea	0	1 (1)	0	0	0
Vomiting	0	1 (1)	1 (1)	0	0
Skin and subcutaneous tissue disorders	**2 (2)**	**2 (3)**	**1 (1)**	**0**	**2 (4)**
Drug eruption	0	1 (1)	0	0	1 (2)
Purpura	0	0	0	0	1 (2)
Toxic skin eruption	0	0	1 (1)	0	1 (2)
Photosensitivity reaction	1 (1)	1 (1)	0	0	0
Erythema nodosum	1 (1)	0	0	0	0
Rash	1 (1)	0	0	0	0
Renal and urinary disorders	**0**	**1 (1)**	**0**	**0**	**0**
Renal failure acute	0	1 (1)	0	0	0
General disorders and administration site conditions	**0**	**0**	**1 (1)**	**1 (1)**	**0**
Asthenia*	0	0	1 (1)	1 (1)	0
Investigations	**0**	**1 (1)**	**1 (1)**	**0**	**0**
Blood potassium	0	0	1 (1)	0	0

	TID16W (N=81)	TID28W (N=80)	TID40W (N=77)	BID28W (N=78)	TID28W-NR (N=46)
decreased					
Electrocardiogram QT prolonged	0	1 (1)	0	0	0
Injury, poisoning and procedural complications	**0**	**1 (1)**	**0**	**1 (1)**	**1 (2)**
Gun shot wound	0	0	0	0	1 (2)
Accident at work	0	1 (1)	0	0	0
Limb traumatic amputation	0	1 (1)	0	0	0
Radius fracture	0	0	0	1 (1)	0

* Loss or lack of bodily strength

Table S5. Frequency of patients with Division of Acquired Immunodeficiency Syndrome, National Institutes of Health (DAIDS) Grades 2, 3, and 4 Safety Laboratory Changes Worst Grade on Treatment

	TID16W (N=81)	TID28W (N=80)	TID40W (N=77)	BID28W (N=78)	TID28W-NR (N=46)
Hemoglobin					
Grade 2	4 (5)	5 (6)	6 (8)	10 (13)	0
Grade 3	0	2 (3)	3 (4)	1 (1)	0
Grade 4	0	0	0	1 (1)	0
White blood cells					
Grade 2	0	0	0	1 (1)	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Platelets					
Grade 2	0	2 (3)	2 (3)	0	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
ALT					
Grade 2	0	2 (3)	2 (3)	0	1 (2)
Grade 3	1* (1)	0	0	1* (1)	0
Grade 4	0	0	0	0	0
Total bilirubin†					
Grade 2	19 (23)	31 (39)	24 (31)	27 (35)	10 (22)
Grade 3	33 (41)	15 (19)	20 (26)	20 (26)	6 (13)
Grade 4	4 (5)	10 (13)	5 (6)	10 (13)	0

*Both patients had isolated grade 3 elevations of ALT that normalized on treatment without concomitant conjugated bilirubin increases.

†All patients with total bilirubin Grade 2 or worse except four had unconjugated hyperbilirubinemia (conjugated:total bilirubin ratio <0.5); two patients (TID28W) experienced Grade 2 and two (TID40W and TID28W-NR) experienced Grade 3. Neither patient with Grade 3 discontinued due to hyperbilirubinemia.