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VIRAL HEPATITIS

DAUPHINE: a randomized phase II study of danoprevir/ritonavir plus peginterferon alpha-2a/ribavirin in HCV genotypes 1 or 4

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Keywords
danoprevir – hepatitis C virus – response-guided therapy – ritonavir-boosting – sustained virological response

Abbreviations
AE, adverse event; ALT, alanine aminotransferase; BID, twice daily; BMI, body mass index; CI, confidence interval; Danoprevir/r, ritonavir-boosted danoprevir; eRVR2, extended rapid virological response; HCV, hepatitis C virus; ITT, intent-to-treat; LLOD, lower limit of detection; P/R, peginterferon alpha-2a/ribavirin; RGT, response-guided therapy; SAE, serious adverse event; SD, standard deviation; SVR, sustained virological response; ULN, upper limit of normal.

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Abstract

Background & Aims: Danoprevir is a hepatitis C virus (HCV) protease inhibitor with activity against genotypes (G)1/G4, which is maintained at lower doses by ritonavir-boosting. We report results of a large, randomized, active-controlled phase IIb study of ritonavir-boosted danoprevir (danoprevir/r) plus peginterferon alpha-2a/ribavirin (P/R) in treatment-naive patients with HCV G1/4 infection. *Methods:* Treatment-naive patients with HCV G1/4 infection were randomized to twice-daily danoprevir/r 200/100 mg (A, $n = 92$); 100/100 mg (B, $n = 93$); or 50/100 mg (C, $n = 94$) plus P/R for 24 weeks; twice-daily danoprevir/r 100/100 mg (D, $n = 94$) plus P/R for 12 or 24 weeks; or P/R alone (E, $n = 44$) for 48 weeks. Patients in the response-guided therapy arm (D) with an extended rapid virological response (eRVR2: HCV RNA <15 IU/ml during Weeks 2–10) stopped all therapy at Week 12; non-eRVR2 patients continued all treatment to Week 24. The primary efficacy endpoint was sustained the virological response (SVR24: HCV RNA <15 IU/ml after 24 weeks of untreated follow-up). *Results:* SVR24 rates in Arms A, B, C, D and E were 89.1%, 78.5%, 66.0%, 69.1% and 36.4%, respectively, in the overall population; 83.6%, 69.6%, 60.3%, 59.2% and 38.5% in G1a-infected patients, 96.6%, 93.1%, 73.1%, 78.4% and 28.6% in G1b-infected patients and 100%, 87.5%, 100%, 100% and 66.7% in G4-infected patients. Danoprevir/r plus P/R was generally well tolerated compared with P/R alone. There was a higher incidence of serious adverse events in danoprevir-treatment arms, but most were associated with P/R. *Conclusions:* The combination of danoprevir/r plus P/R is efficacious in treatment-naïve patients with HCV genotype 1 or 4 infection.

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The current standard of care for patients who are chronically infected with the hepatitis C virus (HCV) genotype 1 is triple therapy with peginterferon alpha plus ribavirin and either boceprevir or telaprevir (1). In treatment-naive patients, the advantages of triple therapy are an approximately 30% improvement in sustained virological response (SVR) compared with treatment with peginterferon/ribavirin alone, plus the ability to limit the duration of therapy to 24 weeks in 44–65% of patients (2–4). Despite the improvements in virological response rates, current triple therapy has several disadvantages. Both boceprevir and telaprevir add adverse events to those observed with peginterferon/ribavirin (2–4). Telaprevir increases the risk for rash, which can be severe and require treatment discontinuation, and both telaprevir and boceprevir increase the risk for clinically significant anaemia. Moreover, neither boceprevir nor telaprevir have demonstrated activity against HCV genotype 4 (2, 3, 5, 6). In addition, four pills of boceprevir or two pills of telaprevir must be administered thrice daily (5, 6) – the complexity of dosing and pill burden are potential deterrents to treatment.

Given the pitfalls of current triple therapy, there is need for alternative direct-acting antiviral agents that are more potent, convenient to administer, better tolerated and that have a broader spectrum of activity. Danoprevir (RG7227, ITMN-191) is a second-generation, macrocyclic inhibitor of the NS3/4a protease of HCV and has equipotent activity against HCV genotypes 1, 4, and 6 *in vitro* (7, 8). In a phase II study of treatment-naive patients, danoprevir in combination with peginterferon/ribavirin achieved rates of SVR of up to 85% (9). However, high doses of danoprevir (1200/1800 mg daily) were associated with Grade 4 alanine aminotransferase (ALT) elevations (9). The mechanism of danoprevir hepatotoxicity was linked to the formation of reactive metabolites at high doses through the action of hepatic CYP3A4 (10). Subsequent studies indicated that co-administration of ritonavir, which irreversibly binds to and inhibits CYP3A4, could allow for the use of lower doses of danoprevir, maintain virological response and block the formation of reactive metabolites (11). In a multiple ascending dose trial of ritonavir-boosted danoprevir (danoprevir/r), all patients experienced a 5-$\log_{10}$ decline in HCV RNA after 15 days of treatment and up to 69% of patients had undetectable HCV RNA (<15 IU/ml) by Day 9 (12). None experienced ALT elevations.

Here we report the results of the DAUPHINE trial: a large, randomized, active-controlled, phase IIb study of the efficacy, safety and tolerability of danoprevir/r in combination with peginterferon alpha-2a/ribavirin in treatment-naive patients with HCV genotype 1 or 4 infection.

Patients and methods

Patients

Eligible patients were treatment-naive, aged 18 years or older, and had chronic HCV genotype 1 or 4 infection with an HCV RNA level ≥50 000 IU/ml. All patients had a liver biopsy within 24 months of enrolment with histological evidence of chronic hepatitis C. Patients with cirrhosis or incomplete/transition to cirrhosis (Knodell, Metavir, or Batts and Ludwig ≥3 or Ishak modified HAI ≥4) and those with a body mass index (BMI) <18 or ≥36 kg/m^2 were excluded, as were patients with other forms of liver disease, HIV infection, hepatocellular carcinoma, severe cardiac disease, severe depression or other psychiatric disease, renal disease, uncontrolled seizure disorders or severe retinopathy. Laboratory criteria for enrolment included haemoglobin ≥12 g/dl for women or ≥13 g/dl for men; neutrophil count ≥1.5 × 10^9 cells/L; platelet count ≥90 × 10^9 cells/L; and serum creatinine ≤1.5 times the upper limit of normal (ULN). Use of medications or nutrients that could interfere with the metabolism of danoprevir or ritonavir was prohibited.

Pregnant females and male patients with pregnant partners were excluded. Female patients of childbearing potential and male patients with female partners of childbearing potential were required to use two forms of non-hormonal contraception during treatment and for at least 24 weeks following the last dose of danoprevir/r and ribavirin.

Study design

This was a randomized, open-label, multicenter, parallel-group phase IIb study (ClinicalTrials.gov: NCT01220947). Patients were randomized (2:2:2:2:1) to one of five treatment arms, A through E. Patients in Arms A, B and C were treated for 24 weeks with peginterferon alpha-2a (40KD) (PEGASYS®, Roche, Basel, Switzerland) 180 μg/week and ribavirin (COPEGUS®, Roche, Basel, Switzerland) 1000 mg/day (bodyweight <75 kg) or 1200 mg/day (bodyweight ≥75 kg) plus danoprevir/r at doses of 200/100 mg BID (Arm A), 100/100 mg BID (Arm B), or 50/100 mg BID (Arm C). Patients in Arm D received response-guided therapy (RGT) with peginterferon alpha-2a/ribavirin plus danoprevir/r 100/100 mg BID. Patients achieving undetectable HCV RNA from Weeks 2 to 10 (extended rapid virological response, eRVR2) stopped treatment at Week 12. Patients without an eRVR2 were treated for 24 weeks. Patients in the control arm (E) received peginterferon alpha-2a plus ribavirin for 48 weeks according to the label (Fig. S1). Patients in Arm E with detectable HCV RNA at Week 12 had the option to roll over to treatment with danoprevir/r 200/100 mg BID plus peginterferon alpha-2a/ribavirin.

Randomization was centralized and stratified by host *IL28B* rs12979860 genotype (CC vs. non-CC as determined by Sanger sequencing by Gentris Corporation, Morrisville, NC, USA) and by geographical region (European countries and Brazil vs. USA, Canada, and Mexico). The computer-generated randomization list was maintained by the sponsor and study sites were informed of patient assignments by an interactive voice/interactive web response system.

Stepwise reductions in the dose of peginterferon alpha-2a (in 45 μg decrements) and ribavirin (in 200 mg decrements) were permitted to manage adverse events or laboratory abnormalities. Dose modifications of danoprevir/r were not allowed, although interruptions to manage adverse events were allowed.

Patients prematurely discontinuing danoprevir/r were allowed to continue treatment with peginterferon alpha-2a/ribavirin. Patients prematurely discontinuing peginterferon alpha-2a were required to stop all other study medication. If patients were required to prematurely discontinue danoprevir/r and ribavirin, they could remain on peginterferon alpha-2a monotherapy for the remainder of the treatment period. Use of hematopoietic growth factors (e.g. erythropoietin-stimulating agents, granulocyte-colony stimulating factors) was not recommended by the sponsor, but was permitted at the discretion of the investigator.

Stopping rules

Patients were required to discontinue danoprevir/r if they had a $<1-\log_{10}$ decrease in HCV RNA at Week 4 of treatment or if they experienced virological breakthrough or a partial response (as defined below). Patients in Arms A–D with detectable HCV RNA (≥15 IU/ml) at Week 12 of treatment were required to discontinue all treatments. Patients in the control arm (E) with detectable HCV RNA at Week 12 and with a $<1-\log_{10}$ decrease in HCV RNA level at Week 12 were required to discontinue all treatments. Treatment with danoprevir/r was also to be discontinued in the event of any new onset Grade 4 ALT elevation, or a Grade 3 ALT elevation in combination with a Grade 2 bilirubin elevation.

Ethics

This study was conducted in full conformity with the principles of the Declaration of Helsinki, Good Clinical Practice and the EU Clinical Trial Directive (2001/20/EC). The protocol and all amendments were reviewed and approved by the institutional review boards at each study site. All patients provided written informed consent before undergoing any study procedures. All authors have had access to the study data and have reviewed and approved the final manuscript.

Efficacy assessments

HCV RNA levels were quantified by the Roche COBAS TaqMan® HCV Test (lower limit of detection [LLOD] = 15 IU/ml) (Roche Diagnostics, Indianapolis, IN, USA) at baseline and at Weeks 1 and 2, then every 2 weeks through to Week 24, then every 6 weeks through to Week 48 of treatment and at Weeks 2, 4, 8, 12 and 24 of untreated follow-up. SVR24 was defined as undetectable HCV RNA (<15 IU/ml, target not detected) 24 weeks after the end of treatment. Relapse was defined as undetectable HCV RNA at the end of treatment followed by detectable HCV RNA during follow-up. HCV genotyping and subtyping were performed by Cenetron Diagnostics, Cedar Creek, Texas.

Safety assessments

Safety was assessed at each clinic visit by vital signs, laboratory tests (haematology, chemistry and urinalysis), clinical adverse events, dose modifications and treatment discontinuations related to adverse events or laboratory abnormalities.

Resistance monitoring

Viral load kinetics were monitored throughout this study. Baseline treatment and post-treatment samples from all patients who experienced virological breakthrough, partial response, non response, or relapse were tested for viral resistance.

Virological breakthrough was defined as a sustained $\geq 1-\log_{10}$ IU/ml increase in HCV RNA level or confirmed quantifiable HCV RNA in patients who previously had confirmed undetectable HCV RNA. Partial response was defined as viral load stabilization (defined as an HCV RNA level within $0.5-\log_{10}$ of nadir for at least two consecutive measurements) after a decrease in HCV RNA of $\geq 0.5-\log_{10}$ IU/ml and/or an HCV RNA level ≥1000 IU/ml by the end of at least 4 weeks of danoprevir/r treatment. Non-response was defined as a $<0.5-\log_{10}$ decrease in HCV RNA from baseline after 2 weeks of treatment. Viral variants resistant to danoprevir were detected by population sequencing of the complete HCV NS3/4A coding region using standard technology as described previously (13).

Statistical considerations

The primary efficacy outcome was the proportion of patients with an SVR24 (undetectable HCV RNA at 24 weeks after the last dose). Analysis of efficacy was based upon a modified intent-to-treat (ITT) population that included all randomized patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment. Patients with missing SVR24 results were considered to be non-responders in the primary analysis. The target sample size was 405

patients with a distribution of 90 in each of the four danoprevir/r-treatment arms, and 45 in the peginterferon alpha-2a/ribavirin control arm. The sample size of 90 patients was expected to provide a 95% confidence interval (CI) with a 10% margin of error assuming an expected SVR rate of 65%. No formal statistical pairwise comparisons were planned. Ninety-five per cent confidence intervals for SVR rates were calculated using the Wilson method (14, 15).

A *post hoc* sensitivity analysis was performed to assess the impact of missing data on SVR. Patients with undetectable HCV RNA (<15 IU/ml) at their last visit who did not have at least an SVR12 assessment were excluded from this analysis. Patients who died during this study were considered to be non-responders in the sensitivity analysis.

The safety population included all randomized patients who received at least one dose of study medication and had at least one post-baseline safety assessment.

Results

The first patient was enrolled on 11 November 2010 and the last patient completed follow-up on 20 August 2012. A total of 574 patients from 73 sites across Brazil, Canada, Mexico, the USA and Europe were screened for enrollment, of whom 421 patients were randomized and 417 received at least one dose of study medication (Fig. 1). Baseline demographics were similar across treatment and control groups (Table 1). Mean age was 48 years, 62% were male, mean BMI was 26 kg/m^2 and 9% were black. Fifty-nine per cent were infected with HCV genotype 1a, 32% with genotype 1b, and 8% with genotype 4. One patient with HCV genotype 3 was randomized and treated with danoprevir/r 50/100 mg BID in Arm C. Seventy-one per cent had a non-CC *IL28B* genotype, and the mean baseline HCV RNA level was 6.3−$\log_{10}$ IU/ml. Fifty-eight per cent, 41% and 2% of patients had stage F0/F1, F2 and F3 fibrosis respectively (Table 1).

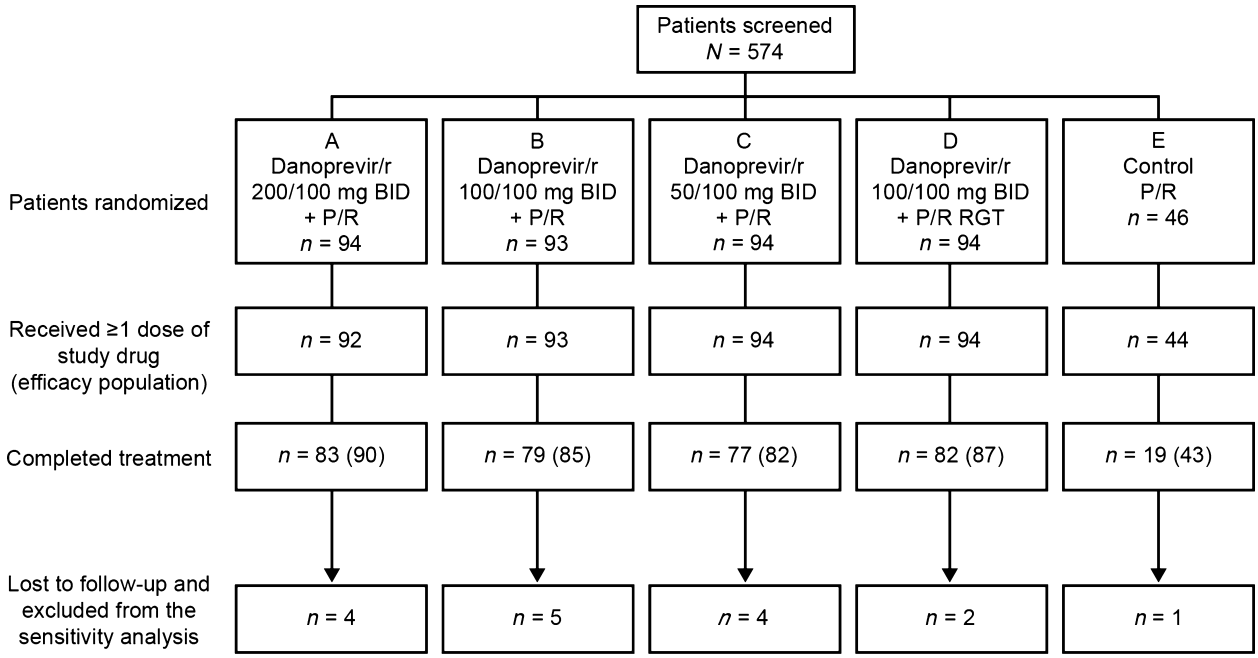


Fig. 1. Patient flow diagram.

Table 1. Baseline characteristics (efficacy population)

	A Danoprevir/r 200/100 mg BID + P/R (24 weeks) *n* = 92	B Danoprevir/r 100/100 mg BID + P/R (24 weeks) *n* = 93	C Danoprevir/r 50/100 mg BID + P/R (24 weeks) *n* = 94	D Danoprevir/r 100/100 mg BID + P/R (12/24 weeks) RGT *n* = 94	E P/R Control (48 weeks) *n* = 44
Male, *n* (%)	57 (62)	56 (60)	67 (71)	58 (62)	22 (50)
Median age (range), years	46.0 (19–64)	52.0 (22–73)	50.5 (20–66)	48.0 (18–67)	51.0 (19–64)
Race, *n* (%)					
White	72 (78)	80 (86)	74 (79)	86 (91)	33 (75)
Black	9 (10)	8 (9)	11 (12)	5 (5)	6 (14)
Other	11 (12)	5 (5)	9 (10)	3 (3)	5 (11)
Mean BMI, kg/m^2 ± SD	25.9 ± 4.0	26.9 ± 4.4	26.1 ± 3.9	25.9 ± 3.7	26.9 ± 4.8
Mean HCV RNA level, log_{10} IU/ml ± SD	6.3 ± 0.7	6.3 ± 0.8	6.5 ± 0.7	6.3 ± 0.7	6.3 ± 0.8
HCV genotype, *n* (%)					
1a	55 (60)	56 (60)	58 (62)	49 (52)	26 (59)
1b	29 (32)	29 (31)	26 (28)	37 (39)	14 (32)
1 (other subtype or not typed)	0	0	2 (2)	1 (1)	1 (2)
4	8 (9)	8 (9)	7 (7)	7 (7)	3 (7)
3	0	0	1 (1)	0	0
Host *IL28B* genotype, *n* (%)					
CC	28 (30)	27 (29)	27 (29)	25 (27)	12 (27)
non-CC	64 (70)	66 (71)	67 (71)	69 (73)	32 (73)
Fibrosis score, *n* (%)					
0	11 (12)	9 (10)	10 (11)	7 (7)	7 (16)
1	37 (40)	40 (43)	44 (47)	52 (55)	22 (51)
2	44 (48)	42 (45)	39 (41)	32 (34)	13 (30)
3	0	2 (2)	1 (1)	3 (3)	1 (2)

BID, twice daily; BMI, body mass index; P/R, peginterferon alpha-2a plus ribavirin; RGT, response-guided therapy; SD, standard deviation.

Efficacy

The percentage of patients with undetectable HCV RNA at Weeks 1, 2, 4, 12 and 24 was consistently higher in patients in Arms A, B, C and D than in the control arm (Arm E) (Fig. 2). In Arm D (RGT), 59.6% (56/94) of patients achieved an eRVR2.

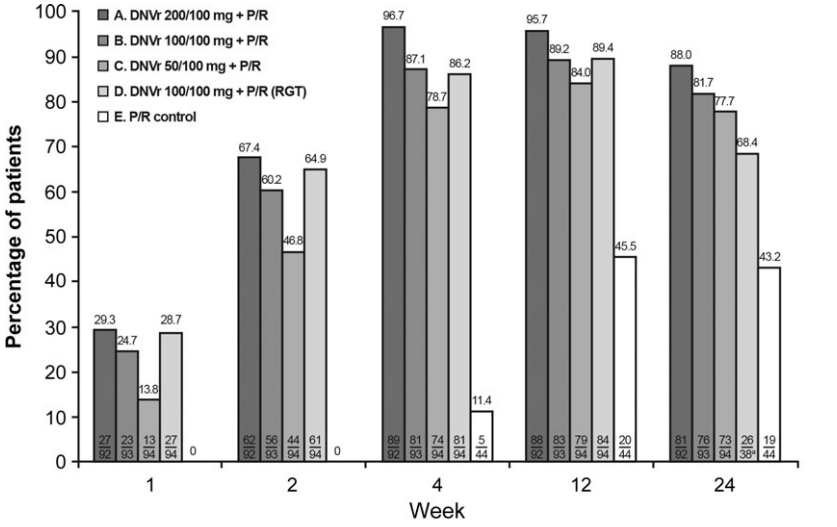
Overall rates of SVR24 in the efficacy population were 89.1% (95% CI, 81.1–94.0), 78.5% (95% CI, 69.1–85.6), 66.0% (95% CI, 55.9–74.7) and 69.1% (95% CI, 59.2–77.6) in Arms A, B, C and D respectively (Fig. 3A). In comparison, the SVR24 rate was 36.4% (95% CI, 23.8–51.1) in the control arm. In the RGT arm (Arm D) the SVR rate was 71.4% in patients with an eRVR2 and 65.8% in patients without an eRVR2.

Overall relapse rates 24 weeks after end of treatment in Arms A–E were 1.2%, 8.4%, 18.2%, 25.0% and 20.0% (Fig. 3B). Relapse rates in patients in Arm D were 26.8% in those with an eRVR and 21.9% in those without an eRVR2.

A dose–response relationship for danoprevir/r was observed for SVR24 rates in HCV genotype 1a- and 1b-infected patients (Fig. 4A and B). Overall SVR24 rates were consistently higher in patients infected with HCV genotype 1b than 1a in each danoprevir/r-treatment arm, although differences in SVR24 rates between HCV genotype 1a- and 1b-infected patients across the four danoprevir/r-treatment arms were less pronounced in those with a host-*IL28B* CC genotype (Table 2).

SVR24 rates in patients with a CC or non-CC *IL28B* genotype are shown in Fig. 4C and D. Rates of SVR24 in Arms A–E were 96.4%, 81.5%, 81.5%, 92.0% and 58.3% for patients with an *IL28B* CC genotype and 85.9%, 77.3%, 59.7%, 60.9% and 28.1% in those with non-CC genotypes.

A total of 29 (96.7%) of 30 genotype 4-infected patients achieved an SVR24 after treatment with danoprevir/r across all treatment arms (Fig. 4E One genotype 4 patient in Arm D was temporarily lost to follow-up after Week 8 and did not receive further treatment, but did achieve an SVR24. The one genotype 4 patient who did not achieve SVR24 (in Arm B) was HCV RNA-negative 4 weeks after stopping treatment, but was then lost to follow-up. All but one patient with an *IL28B* CC genotype and HCV genotype 1b infection achieved an SVR24 in the four danoprevir/r arms (32/33 patients overall). In the highest-dose arm (A) SVR24 rates among *IL28B* CC patients were 100% and 94.7% in the HCV genotype 1b and 1a subgroups respectively. Among patients with an eRVR2 treated with the abbreviated regimen, the SVR24 rate was 100% (6/6) in genotype 4-infected patients and 90% (18/20) in patients with a CC genotype. SVR24 rates were lower in other subgroups (Table S1).



a. Only patients without an early extended rapid virologic response (HCV RNA <15 IU/mL throughout Weeks 2–10) were included in the calculation of the Week 24 virologic response

DNVr, danoprevir/ritonavir; P/R, peginterferon alfa-2a 180 μg/week plus ribavirin 1000 mg/day or 1200 mg/day; RGT, response-guided therapy

Fig. 2. Virological response over time (ITT analysis, efficacy population).

Sensitivity analysis

Overall, 16 patients were lost to follow-up (Arm A 4; B 5; C 4; D 2; E 1) who had undetectable HCV RNA (<15 IU/ml) at their last visit. When these patients were excluded from the sensitivity analysis, SVR24 rates were 93.2%, 83.0% and 68.9% in Arms A, B and C, respectively, and 37.2% in the control group (E). SVR rates of 72.7% and 67.6% respectively were achieved among patients with and without an eRVR in Arm D. The results of the entire sensitivity analysis were consistent with the modified ITT analysis (Table S2).

Resistance

Baseline population sequencing spanning the NS3/4A region was performed for 408 patients. One genotype 1a patient had an R155K mutation at baseline, and was lost to follow-up after achieving a virological response (HCV RNA <15 IU/ml) at Week 12.

A total of 23 patients experienced virological breakthrough or partial response and 1 patient had a non-response. Virological breakthrough/partial response occurred in 2, 5, 12 and 4 patients in Arms A, B, C and D, respectively, and non-response occurred in 1 patient in Arm A. The danoprevir resistance mutation NS3 R155K was detected in 22/23 patients with breakthrough/partial response (18 genotype 1a; 4 genotype 1b; 1 sample could not be amplified). The patient with a non-response (genotype 1a) had no genotypic/phenotypic resistance to danoprevir at baseline. Forty-one danoprevir/r-treated patients relapsed, with a higher incidence in patients infected with HCV genotype 1a (n = 31). Among the 31 patients with genotype 1a infection who relapsed, R155K mutant virus was detected in 28 individuals, a dual mutation R155K/R-D168D/E was detected in one individual and D168E mutant virus alone was detected in two individuals. A more diverse resistance profile was observed among the 10 patients with genotype 1b infection who relapsed: five patients had mutations at position 168, one patient had a Q80K mutation, two patients had dual mutations at positions 155 and 168 and one patient had no known danoprevir resistance mutations by population sequencing (samples from one patient could not be amplified).

Safety

The incidence of discontinuations from treatment caused by adverse events (AEs) ranged from 2% to 6% across Arms A–E (Table 3). The nature and incidence of AEs and laboratory abnormalities were generally similar between the danoprevir/r plus peginterferon alpha-2a/ribavirin arms and the peginterferon alpha-2a/ribavirin control arm. The most common AEs were headache, fatigue and pyrexia (Table 3). Diarrhoea was the only AE that occurred with an incidence that was at least 10% higher in all danoprevir/r arms than in the control group. The incidence of rash varied widely across the four danoprevir/r arms (16–29%) and was 14% in the control arm. All cases of rash were of mild to moderate severity and none was associated with sequelae.

A total of 28 patients experienced one or more serious AEs (SAEs) during the trial [9 (10%), 8 (9%), 6 (6%), 4 (4%) and 1 (2%) patients, respectively, in Arms A, B, C, D and E]. SAEs in 14 patients were considered to be possibly, probably or remotely related to treatment with one or more study drugs in the opinion of the

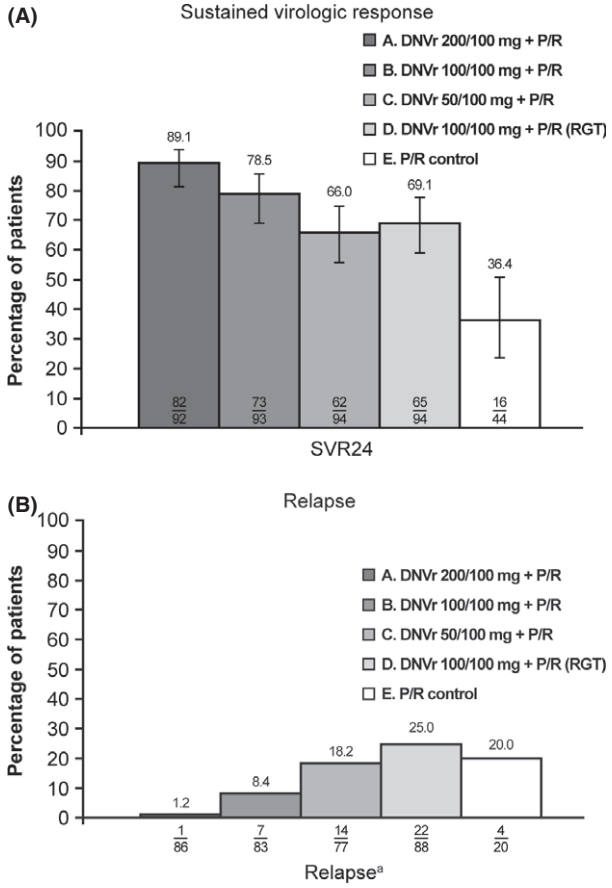


Fig. 3. SVR24 (ITT analysis; efficacy population) and relapse rates. Only patients with an end-of-treatment virological response and at least one post-treatment HCV RNA test result are included in the calculation of relapse. Error bars represent 95% confidence intervals. DNVr, danoprevir/ritonavir; P/R, peginterferon alpha-2a 180 μg/week plus ribavirin 1000 mg/day or 1200 mg/day; RGT, response-guided therapy.

investigator, including four in Arm A, five in Arm B, one in Arm C, three in Arm D and one in Arm E. Two patients experienced SAEs possibly related to danoprevir (pancreatitis and acute renal failure, both in Arm D). Two patients experienced SAEs considered possibly related to peginterferon alpha-2a and danoprevir (pancreatitis and depression, both in Arm B). Six patients experienced SAEs possibly or probably related to peginterferon alpha-2a, including one patient each with sarcoidosis, limb abscess, depression and hypertension in Arm A, one patient with asthenia in Arm B and one patient with a skin infection and neutropenia in Arm C. One patient experienced a hypersensitivity reaction possibly related to ribavirin (Arm E), one experienced abdominal pain possibly related to ritonavir (Arm B) and one patient experienced anaemia probably related to peginterferon alpha-2a/ribavirin (Arm D). A further patient experienced pneumonia that was considered to be possibly related to peginterferon alpha-2a and subsequently, an acute myocardial infarction that was considered to be related to ribavirin (Arm B).

Overall, there were no increases in the incidence of Grade 3 and 4 anaemia, lymphopenia or thrombocytopenia in the danoprevir/r-treatment arms when compared with the control arm. The incidence of Grade 3 and 4 neutropenia was higher in Arm A than in Arms B, C, D and the control arm (Table 2). However, the higher overall rate of neutropenia in Arm A was not associated with an increased rate of serious infections. Only four patients had infections reported as SAEs (two in Arm A and one each in Arms B and C). Two of these individuals [one in Arm A (limb abscess), one in Arm C (skin infection)] experienced Grade 4 neutropenia during treatment; however, the infections resolved with treatment and both patients completed treatment.

No danoprevir/r-related Grade 3 or 4 ALT elevations were reported during treatment. One patient in Arm C (danoprevir/r 50/100 mg) had a reversible Grade 3 elevation in ALT level at Weeks 16 and 24 (the patient was on fenofibrate from Week 4 to Week 3 of follow-up), which normalized upon completion of fenofibrate treatment. This patient completed the planned duration of danoprevir/r treatment at Week 24 and subsequently achieved an SVR24. A Grade 4 ALT elevation occurred in one patient (Arm B; danoprevir/r 100/100 mg) after discontinuation of danoprevir/r because of an insufficient therapeutic response, but during continuation of peginterferon alpha-2a/ribavirin treatment.

Two deaths occurred in Arm B during the trial and were attributed to pneumonia and myocardial infarction in one individual (possibly related to peginterferon alpha-2a treatment and ribavirin, but not danoprevir in the investigator's opinion) and coronary artery disease in a second patient (not related to treatment).

Discussion

The results of this study demonstrate that the combination of danoprevir/r and peginterferon alpha-2a/ribavirin produces rapid and sustained reductions in serum HCV RNA levels and consistently higher SVR24 rates than peginterferon alpha-2a/ribavirin in treatment-naive patients with chronic HCV genotype 1 or 4 infection. In this study, overall SVR24 rates of 89.1% and 78.5% were achieved with danoprevir/r 200/100 mg and 100/100 mg (non-RGT) respectively. The results of the sensitivity analysis were consistent with the primary efficacy analysis: excluding patients lost to follow-up, SVR24 rates of 93.2% and 83.0% were achieved in Arms A and B respectively. The overall SVR rates achieved with the lowest dose of danoprevir/r (50/100 mg) in Arm C and with the RGT strategy in Arm D were less satisfactory.

Patients with a host *IL28B* CC genotype had consistently higher SVR24 rates than patients with a non-CC genotype regardless of danoprevir/r dosage, duration of treatment or HCV genotype or subtype. Moreover, most patients in Arm D with a CC genotype achieved an

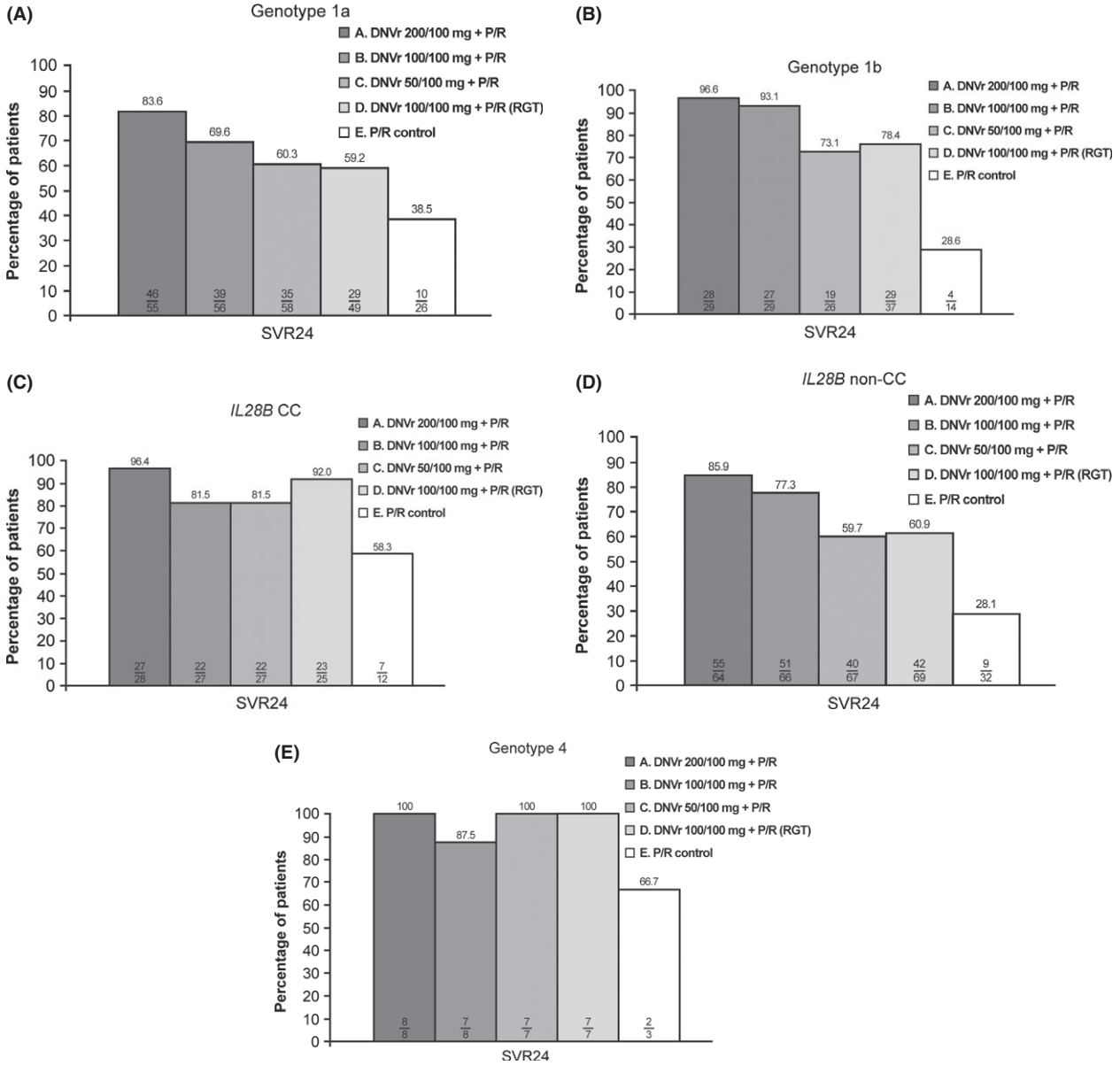


Fig. 4. SVR24 rates according to HCV genotype and subtype and host *IL28B* genotype. DNVr, danoprevir/ritonavir; P/R, peginterferon alpha-2a 180 μg/week plus ribavirin 1000 mg/day or 1200 mg/day; RGT, response-guided therapy.

eRVR2 (80%) and the SVR24 rate in these individuals was 90% with 12 weeks of treatment. Only five genotype CC patients in Arm D did not achieve an eRVR2, but they all achieved an SVR24 after 24 weeks of treatment.

Dose–response relationships were evident when the data were analysed by HCV genotype and subtype. The highest SVR24 rates were achieved in HCV genotype 1b-infected patients with danoprevir/r 200/100 mg BID (96.6%) and 100/100 mg BID (93.1%). The corresponding SVR24 rates in HCV genotype 1a patients were 83.6% and 69.6% respectively.

High SVR24 rates were observed in genotype 1b-infected patients with an *IL28B* CC genotype, including those in the RGT Arm. Only 1 HCV genotype 1b/*IL28B* CC patient did not achieve an SVR24 across all danoprevir/r-treatment arms and, when patients lost to follow-up were excluded in the sensitivity analysis, all achieved an SVR24. In contrast to genotype 1b-infected patients with an *IL28B* CC genotype, a strong dose–response relationship was observed in the more challenging-to-treat patient subgroup with genotype 1a infection and an *IL28B* non-CC genotype.

Few historical data are available on the response to peginterferon alpha/ribavirin by HCV genotype 1 subtype. Among patients in the peginterferon alpha-2a/ribavirin control group (Arm E), SVR24 rates were

Table 2. SVR24 rates according to HCV genotype and subtype and host *IL28B* genotype (efficacy population). Data are presented as n/N (%, 95% confidence interval)

	A	B	C	D		E
	Danoprevir/r 200/100 mg BID + P/R $n = 92$	Danoprevir/r 100/100 mg BID + P/R $n = 93$	Danoprevir/r 50/100 mg BID + P/R $n = 94$	Danoprevir/r 100/100 mg BID + P/R RGT		P/R Control $n = 44$
				eRVR $n = 56$	No eRVR $n = 38$	
IL28B CC and genotype 1a	18/19 (94.7%, 75.4–99.1%)	13/16 (81.3%, 57.0–93.4%)	13/18 (72.2%, 49.1–87.5%)	9/11 (81.8%, 52.3–94.9%)	1/1 (100%, 20.7–100%)	4/7 (57.1%, 25.0–84.2%)
IL28B CC and genotype 1b	8/8 (100%, 67.6–100%)	6/7 (85.7%, 48.7–97.4%)	7/7 (100%, 64.6–100%)	7/7 (100%, 64.6–100%)	4/4 (100%, 51.0–100%)	2/4 (50%, 15.0–85.0)
IL28B non-CC and genotype 1a	28/36 (77.8%, 61.9–88.3%)	26/40 (65.0%, 49.5–77.9%)	22/40 (55.0%, 39.8–69.3%)	8/16 (50.0%, 28.0–72.0%)	11/21 (52.4%, 32.4–71.7%)	6/19 (31.6%, 15.4–54.0)
IL28B non-CC and genotype 1b	20/21 (95.2%, 77.3–99.2%)	21/22 (95.5%, 78.2–99.2%)	12/19 (63.2%, 41.0–80.9%)	10/16 (62.5%, 38.6–81.5%)	8/10 (80.0%, 49.0–94.3%)	2/10 (20.0%, 5.7–51.0)

BID, twice daily; P/R, peginterferon alpha-2a plus ribavirin; RGT, response-guided therapy.

lower in patients with HCV genotype 1b than 1a infection (29% vs. 39%). Although perhaps lower than one might expect, this pattern of SVR24 rates is similar to that obtained with the same regimen in the control group of a previous study (33% and 48%, in patients with genotype 1b and 1a infection respectively) (9).

The results in the various subgroups defined by host genotype and viral genotype/subtype must be interpreted with caution because of small patient numbers in each arm; however, the data indicate that a shorter treatment duration of 12 weeks with danoprevir/r plus peginterferon alpha-2a/ribavirin is as effective as a 24-week regimen in patients with a CC *IL28B* host genotype and in those with a HCV genotype 4 infection.

The overall SVR24 rate of 89% achieved with danoprevir/r 200/100 mg plus peginterferon alpha-2a/ribavirin in this study is higher than that reported in phase III trials of the first-generation protease inhibitors, boceprevir (63–66%) and telaprevir (72–75%), in treatment-naive HCV genotype 1-infected patients (2–4). However, it must be noted that this study excluded patients with cirrhosis and enrolled very few with bridging fibrosis, thus a direct comparison of SVR rates from these trials is not possible. Among second-generation protease inhibitors in late-stage clinical development, SVR24 rates of 75–86% (vs. 65% with peginterferon alpha-2a/ribavirin) and 71–83% (vs. 56%) were obtained with 24 weeks of simeprevir (TMC435) and faldaprevir (BI 201335), respectively, in combination with peginterferon alpha-2a/ribavirin in phase II studies (16–18). Twelve weeks' treatment with the combination of sofosbuvir (nucleoside analogue HCV protease inhibitor) plus peginterferon/ribavirin has been reported to produce SVR rates of 89% in HCV genotype 1-infected patients (19). Direct comparisons between SVR24 rates observed in clinical trials of danoprevir/r and other direct-acting antiviral agents are limited by the absence of head-to-head studies, as well as by differences in study designs, patient characteristics and criteria for defining on-treatment virological responses.

The combination of danoprevir/r plus peginterferon alpha-2a/ribavirin was safe and well tolerated through 24 weeks. In general, the nature and incidence of AEs was typical of that associated with peginterferon alpha-2a/ribavirin in this study and in previous studies (20, 21). Moreover, the incidence of AEs did not appear to be dose-related across the danoprevir-treatment arms (A–D). No increases in the incidence of rash or anaemia were observed in the danoprevir/r-treatment arms (A–D) relative to the peginterferon alpha-2a/ribavirin control arm (E) and rash was not reported as an SAE in any patient. Most of the SAEs considered to be possibly related to treatment by investigators were associated with peginterferon alpha-2a and or ribavirin (in 11 of 14 patients). Five patients experienced SAEs considered to be possibly related to danoprevir and or ritonavir.

With the exception of neutropenia, the incidence and severity of laboratory abnormalities (anaemia,

Table 3. Adverse events, dose modifications and laboratory abnormalities (safety population)

	A Danoprevir/r 200/100 mg BID + P/R (24 weeks) *n* = 92	B Danoprevir/r 100/100 mg BID + P/R (24 weeks) *n* = 93	C Danoprevir/r 50/100 mg BID + P/R (24 weeks) *n* = 94	D Danoprevir/r 100/100 mg BID + P/R (12/24 weeks) RGT *n* = 94	E P/R Control (48 weeks) *n* = 44
Patients with ≥1 AE, *n* (%)	89 (97)	90 (97)	93 (99)	92 (98)	42 (95)
Patients with ≥1 SAE, *n* (%)	9 (10)	8 (9)	6 (6)	4 (4)	1 (2)
Number of AEs	840	811	838	707	366
Deaths, *n* (%)	0	2 (2)*	0	0	0
Individual AE, %†					
Headache	45 (49)	38 (41)	37 (39)	38 (40)	24 (55)
Fatigue	43 (47)	41 (44)	38 (40)	36 (38)	17 (39)
Pyrexia	27 (29)	28 (30)	37 (39)	33 (35)	15 (34)
Insomnia	25 (27)	26 (28)	29 (31)	22 (23)	16 (36)
Nausea	33 (36)	24 (26)	26 (28)	23 (24)	13 (30)
Diarrhoea	30 (33)	27 (29)	28 (30)	20 (21)	5 (11)
Pruritus	23 (25)	23 (25)	23 (24)	14 (15)	14 (32)
Myalgia	26 (28)	18 (19)	26 (28)	23 (24)	13 (30)
Rash	20 (22)	27 (29)	16 (17)	15 (16)	6 (14)
Chills	18 (20)	24 (26)	25 (27)	22 (23)	8 (18)
Decreased appetite	23 (25)	17 (18)	25 (27)	23 (24)	6 (14)
Cough	15 (16)	14 (15)	21 (22)	12 (13)	12 (27)
Arthralgia	13 (14)	23 (25)	19 (20)	17 (18)	9 (20)
Alopecia	18 (20)	12 (13)	10 (11)	14 (15)	4 (9)
Asthenia	18 (20)	22 (24)	16 (17)	21 (22)	9 (20)
Laboratory abnormalities, *n* (%)					
Haemoglobin					
Grade 3 (7.0–8.9 g/dl, or any decrease ≥4.5 g/dl	8 (9)	7 (8)	8 (9)	3 (3)	4 (9)
Grade 4 (<7.0 g/dl)	0	0	0	1 (1)	0
Neutrophils					
Grade 3 (0.5–0.749 × 10^9/L)	23 (25)	15 (16)	15 (16)	22 (23)	12 (27)
Grade 4 (<0.5 × 10^9/L)	12 (13)	6 (6)	8 (9)	6 (6)	–
Lymphocytes					
Grade 3 (0.35–0.499 × 10^9/L)	2 (2)	4 (4)	5 (5)	5 (5)	6 (14)
Grade 4 (<0.35 × 10^9/L)	2 (2)	4 (4)	3 (3)	1 (1)	0
Platelets					
Grade 3 (25–<50 × 10^9/L)	2 (2)	1 (1)	2 (2)	2 (2)	1 (2)
Grade 4 (<25 × 10^9/L)	0	0	0	0	0
ALT elevations					
Grade 3 (≥5.1–10.0 × ULN)	2 (2)	2 (2)	2 (2)	2 (2)	2 (5)
Grade 4 (≥10.0 × ULN)	0	1 (1)	0	0	0
Withdrawal for AEs, *n* (%)					
Danoprevir/r	5 (5)	7 (8)	3 (3)	5 (5)	NA
Peginterferon alpha-2a	5 (5)	6 (6)	3 (3)	4 (4)	1 (2)
Ribavirin	5 (5)	7 (8)	3 (3)	4 (4)	1 (2)
Dose modifications, *n* (%)					
Danoprevir/r‡	4 (4)	3 (3)	4 (4)	1 (1)	NA
Peginterferon alpha-2a	6 (7)	4 (4)	6 (6)	2 (2)	2 (5)
Ribavirin	8 (9)	16 (17)	10 (11)	5 (5)	9 (20)

AE, adverse events; BID, twice daily; NA, not applicable; P/R, peginterferon alpha-2a plus ribavirin; RGT, response-guided therapy; SAE, serious AE; ULN, upper limit of normal.

*Causes of death were listed as pneumonia (possibly related to treatment) and coronary artery disease (unrelated to treatment).

†Events reported in ≥20% of patients in ≥1 danoprevir/r-treatment arm (A–D).

‡Patients in whom danoprevir/r-treatment was interrupted to manage adverse events.

lymphocytopenia, and thrombocytopenia) was similar across the four danoprevir/r-treatment arms and in the control arm in this study, and was similar to that expected in patients treated with peginterferon alpha-2a/ribavirin. Grade 4 neutropenia was reported in the four danoprevir/r-treatment arms, with the highest incidence in arm A; however, the low rates of serious infections suggests that neutropenia associated with

danoprevir/r is not of great clinical significance. The absence of Grade 4 neutropenia in the control arm in this study is unusual; rates of Grade 4 neutropenia have ranged 3%–6% in prior studies with the same dosage regimen of peginterferon alpha-2a/ribavirin (21–24).

In a previous phase II study, danoprevir was associated with dose-related Grade 4 ALT elevations (9). No danoprevir/r treatment-related Grade 3 or 4 ALT elevations were observed in the present trial. These results are also consistent with those of other studies of danoprevir/r, in which no serious ALT elevations have been observed (25–27).

Treatment with danoprevir/r in combination with peginterferon alpha-2a/ribavirin was associated with a low incidence (6%) of virological breakthrough, partial response and non-response through 24 weeks. Emergence of resistance to danoprevir was less frequent among patients with HCV genotype 1b than 1a infection, consistent with the higher genetic barrier to danoprevir resistance previously observed with genotype 1b (5, 6). All cases of virological breakthrough/partial response (with available sequence data) were associated with the emergence of resistance to danoprevir, which occurred predominantly through the NS3 R155K substitution and in the lower (50/100 mg) danoprevir/r dose arm. Danoprevir-resistant variants were also found in all but one patient who relapsed (of those with available sequence data). The danoprevir resistance mutation R155K was found predominantly in patients with genotype 1a infection who relapsed (90% of cases), whereas a mutation at position 168 alone or combined with a mutation at position 155 was found in patients with genotype 1b who relapsed (90% of cases).

In conclusion, the results of the phase II DAUPHINE study demonstrate that ritonavir-boosted danoprevir in combination with peginterferon alpha-2a/ribavirin is an efficacious, and generally well-tolerated regimen that is highly effective in treatment-naive patients infected with HCV genotypes 1a, 1b or 4. This study shows that a 24-week regimen of danoprevir/r plus peginterferon alpha-2a/ribavirin produces high SVR24 rates overall and in patients with HCV genotype 1a infection or a host *IL28B* non-CC genotype. Most importantly, a treatment duration of 12 weeks with danoprevir/r plus peginterferon alpha-2a/ribavirin may be sufficient to achieve an SVR24 in patients with an *IL28B* CC genotype, and in patients with HCV genotype 4 infection. Further studies of this regimen in larger randomized clinical trials are warranted.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. SVR24 rates in patients with and without an eRVR2 in arm D according to HCV genotype and subtype and host *IL28B* genotype (efficacy population). Data are presented as *n*/*N* (%, 95% confidence interval).

Table S2. Sensitivity analysis of SVR24 rates. Data are presented as *n*/*N* (%).

Fig. S1. Study design.