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Ritonavir-boosted danoprevir plus peginterferon alfa-2a and ribavirin in Asian chronic hepatitis C patients with or without cirrhosis

Jia-Horng Kao,* Shui-Yi Tung,[†,**] Younjae Lee,[‡] Satawat Thongsawat,[§] Tawesak Tanwandee,[¶] I.-Shyan Sheen,** Jinzi J. Wu,[††] Hui Li,[‡‡] Barbara J. Brennan,[§§] Julian Zhou,[‡‡] Sophie Le Pogam,[¶¶] Isabel Najera,*** James A. Thommes[¶¶] and George Hill[¶¶]

*Graduate Institute of Clinical Medicine and Hepatitis Research Center, National Taiwan University and Hospital, Taipei, [†]Department of Gastroenterology, Chang Gung Memorial Hospital, Chia Yi, **Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Taoyuan, Taiwan; and [‡]Pusan Paik Hospital, Inje University, Pusan, Korea; and [§]Faculty of Medicine, Chiang Mai University, Chiang Mai, [¶]Department of Medicine, Siriraj Hospital, Bangkok, Thailand; and [††]Ascletis BioScience, Hangzhou, [‡‡]Roche Product Development, Shanghai, China; and [§§]Roche Translational and Clinical Research Center, New York, New York, [¶¶]Genentech, South San Francisco, California, USA; and ***Roche Pharma and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, Switzerland

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chronic hepatitis C, danoprevir, peginterferon alfa-2a, ribavirin, virologic response.

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Correspondence
Professor Jia-Horng Kao, Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, 1 Chang-Te St., Taipei 10002, Taiwan.
Email: kaojh@ntu.edu.tw

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Abstract

Background and Aim: Chronic hepatitis C is an important public health problem in Asia. We evaluated the safety, efficacy, and pharmacokinetics of fixed-dose ritonavir-boosted danoprevir plus peginterferon alfa-2a/ribavirin in treatment-naive Asian patients with chronic hepatitis C virus (HCV) genotype (G)1 infection.
Methods: Treatment-naive G1 patients in Taiwan, Thailand, and Korea with serum HCV-RNA level $\geq 10^5$ IU/mL received ritonavir-boosted danoprevir 125/100 mg twice daily plus peginterferon alfa-2a/ribavirin for either 12 (noncirrhotic patients: Arm A, $n = 34$) or 24 weeks (cirrhotic patients: Arm B, $n = 27$) in this phase II open-label study. Sustained virologic response was defined as HCV-RNA < 25 IU/mL 12 weeks after end of treatment (SVR12).
Results: Similar SVR12 rates were achieved in Arms A (88.2%; 95% confidence interval, 73.4–95.3%) and B (88.9%; 71.9–96.2%). Most patients had G1b infection, among whom SVR12 rates in Arms A and B were 96.7% and 91.7%, respectively. The overall SVR12 rate was 94.0% in noncirrhotic Taiwanese patients (100% in the subset of G1b patients). No patients withdrew for safety reasons. Three (11%) cirrhotic patients (Arm B) experienced serious adverse events, none of which was considered to be related to treatment. No Grade 3/4 alanine aminotransferase elevations were reported. The pharmacokinetic properties of danoprevir were broadly overlapping in noncirrhotic and cirrhotic patients both on Days 1 and 14.
Conclusions: Ritonavir-boosted danoprevir plus peginterferon alfa-2a/ribavirin produced sustained virologic response rates $> 90\%$ after 12 weeks' treatment in noncirrhotic and 24 weeks' treatment in cirrhotic Asian patients with G1b infection and was well tolerated. These regimens are well suited to countries where G1b predominates.

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Introduction

Chronic hepatitis C (CHC) is a major global health issue and is a leading cause of cirrhosis, hepatocellular carcinoma, and liver-related death.[1,2] The overall prevalence of CHC in Asia is estimated to be 3.7%, although it varies by country (0.8%, 1.3%, and 4.4% in Korea, China, and Taiwan, respectively).[1] It is estimated that more than 50 million people in East Asia are infected with hepatitis C virus (HCV), predominantly with subgenotype 1 (G1).[1] In China, there are approximately nine million people with active HCV infections, 57% of whom are infected with G1b and $<2\%$ of whom are infected with G1a.[1]

Several direct-acting antivirals (DAAs) are now available in countries outside of Asia for the treatment of CHC. These new agents increase sustained virologic response (SVR) rates and reduce the required duration of therapy when compared with dual-peginterferon alfa/ribavirin therapy.[3,4]

Danoprevir is a second-generation HCV protease inhibitor with potent activity against HCV G1[5] that can be co-administered with low-dose ritonavir to achieve therapeutic danoprevir trough concentrations throughout the dosing interval. Ritonavir lacks anti-HCV activity, but inhibits cytochrome P_{450} 3A4-mediated metabolism of danoprevir allowing for the use of lower danoprevir doses.[5] Ritonavir-boosted danoprevir (danoprevir/r) has been evaluated in combination with peginterferon alfa-2a/ribavirin (danoprevir/r-based triple therapy) for 12 or 24 weeks in treatment-naive G1 patients, most of whom were Caucasian.[6] The combination of danoprevir 100 or 200 mg with ritonavir 100 mg produced consistently high SVR rates in patients infected with HCV G1 and G4, with response rates higher in those with G1b infection compared with G1a and in those with a host interleukin 28B (*IL28B*, rs12979860) CC genotype compared with a non-CC genotype.[6] Given the high prevalence of HCV G1b infection and the large number of patients with an *IL28B* CC genotype in China (84% of G1 patients),[1,7,8] danoprevir/r-based triple therapy seems particularly attractive for clinical evaluation among CHC patients in Asia.

The objective of the DAPSANG study was to evaluate the antiviral activity, safety, and pharmacokinetics of danoprevir/r fixed-dose combination (FDC) plus peginterferon alfa-2a/ribavirin in treatment-naive Asian patients with G1 infection.

Methods

This was a phase II open-label study conducted in primary specialist hepatology clinics in Taiwan, Thailand, and South Korea NCT01749150.

Patients. Treatment-naive adults with CHC G1 infection and a serum HCV-RNA level $\geq 10^5$ IU/mL were eligible for enrollment. Patients with well-compensated cirrhosis (Child-Pugh A) were eligible if the absence of hepatocellular carcinoma had been confirmed within the previous 6 months.

Patients were excluded if they had evidence of HBV or HIV co-infection; a history of decompensated liver disease or chronic liver disease attributable to a cause other than HCV infection and/or a history of serious chronic disease were excluded.

Treatment. All patients received a FDC tablet containing danoprevir/r 125/100 mg twice daily, subcutaneous peginterferon alfa-2a (PEGASYS®, Roche, Basel, Switzerland) 180 μg once weekly, and oral ribavirin (COPEGUS®, Roche, Basel, Switzerland) 1000/1200 mg/day (bodyweight $<75/\geq 75$ kg) in two divided doses. The duration of therapy was 12 weeks in noncirrhotic patients (Arm A), and 24 weeks in cirrhotic patients (Arm B) (Fig. 1). The dose of danoprevir in the FDC formulation was 125 mg, designed to provide danoprevir exposure equivalent to 100 mg when delivered in separate tablets. This was based on unpublished data from a bioavailability study in healthy subjects (NP28136, NCT01592318), showing that the FDC formulation results in 20–30% lower bioavailability for danoprevir compared with separate tablets.

Outcomes. Virologic response was defined as HCV-RNA below the lower limit of quantitation (25 IU/mL) of the Roche COBAS® TaqMan HCV Test v2.0 for High Pure System (Roche, Basel, Switzerland). Rapid virologic response (RVR) was defined as a virologic response at Week 4, and SVR was defined as a virologic response at 12 (SVR12) and 24 weeks (SVR24) after the end of treatment. Relapse was defined as detection of HCV-RNA during follow-up in a patient with an end-of-treatment virologic response.

Safety outcomes included adverse events (AEs), serious AEs (SAEs), and laboratory abnormalities.

The complete coding sequence of the HCV NS3/4A region was analyzed (as described previously[9] by population sequencing in all baseline (predose) samples and samples collected from patients meeting predefined criteria for resistance monitoring (Supplementary Appendix).

Serial blood samples for pharmacokinetic analysis were collected before and after drug administration on Days 1 and 14, and single blood samples were collected predose to determine trough danoprevir concentrations on Days 3, 6, 8, and 12. Pharmacokinetic parameters for danoprevir and ritonavir were estimated using noncompartmental methods using WinNonlin® (Pharsight Corp., Mountain View, CA, USA). Plasma samples were analyzed for danoprevir and ritonavir using validated liquid chromatography-tandem mass spectrometry assays (by inVentive Health Clinical Lab, Inc., Princeton, NJ, USA), the details of which are published elsewhere.[10] The following parameters were estimated in these analyses: maximum concentration (C_{max}), time to C_{max} (t_{max}), area under the concentration–time curve during the dosing interval ($AUC\tau$), trough concentration (C_{min}), apparent volume of distribution (Vd/F), apparent oral clearance (CL/F), and terminal elimination half-life ($t_{1/2}$).

Ethics. The study conformed to the principles of the Declaration of Helsinki, and the laws and regulations of the countries in which it was conducted. The protocol was approved by local institutional review boards, and all patients provided written informed consent.

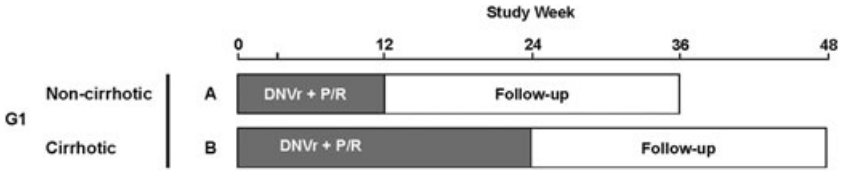


Figure 1 Study design. DNVr FDC, ritonavir-boosted danoprevir fixed-dose combination (125/100 mg twice daily); P, peginterferon alfa-2a 180 μg/week; R, ribavirin (1000 mg [body weight < 75 kg] or 1200 mg [≥ 75 kg] daily in two divided doses). Cirrhosis is defined as Metavir score = 4, Knodell score = 4, Batts & Ludwig score = 4, or Ishak-modified Histology Activity Index score ≥ 5, or as determined by FibroScan® within the past 12 calendar months (cirrhosis is defined as ≥ 14.5 kPa). Patients with an "intermediate reading" (9.5−14.4 kPa) require a liver biopsy to confirm fibrosis score.

Statistics. In this exploratory study, no hypothesis was formally tested, and the sample size was based on clinical judgment and practical considerations. Enrollment of patients with *IL28B* non-CC genotypes was limited to 30% of the total population in order to reflect the genotype distribution in the Asian population. The proportion of patients with virologic responses (and 95% confidence intervals [CI]) was calculated.

Results

A total of 61 patients, including 34 noncirrhotic patients (Arm A) and 27 cirrhotic patients (Arm B), were enrolled at 13 sites in Korea, Thailand, and Taiwan. The first patient was enrolled on March 27, 2013 and the last patient completed follow-up on November 10, 2014.

Most of the patients in Arm A were female (67.6%), whereas the majority of those enrolled in Arm B were male (63.0%) (Table 1). Patients enrolled in Arms A (noncirrhotic) and B (cirrhotic) had a similar mean age (49.1 and 53.2 years, respectively) and mean body mass index (23.2 and 25.5 kg/m^2, respectively), and the majority had an *IL28B* CC genotype (70.6% and 81.5%, respectively) and were infected with G1b (88.2% and 88.9%, respectively) (Table 1).

All patients completed at least 1 week of treatment and 33 of 34 (97.1%) patients enrolled in Arm A, and 24 of 27 (88.9%) patients enrolled in Arm B, completed the assigned treatment duration of 12 and 24 weeks, respectively (Fig. 2). The four patients who withdrew from treatment did so for non-safety reasons (Fig. 2).

Efficacy. Among the 34 noncirrhotic patients in Arm A, 31 (91.2%; CI, 77.0–97.0%) achieved an RVR; 30 (88.2%; CI, 73.4–95.3%) achieved an SVR12, and 29 (85.3%; CI, 69.9–93.6%) achieved an SVR24 (Fig. 3). Among the 27 cirrhotic patients in Arm B, 23 (85.2%; CI, 67.5–94.1%) achieved an RVR, and 24 patients (88.9%; CI, 71.9–96.2%) achieved an SVR12 and SVR24.

Virologic response rates were consistently higher in patients infected with G1b than G1a in both treatment arms, although the number of patients with G1a infection was quite small. Among patients in Arm A with G1b infection, an SVR12 was obtained in 29 of 30 patients (96.7%) (Fig. 4a) and in one of four patients (25.0%) with G1a infection. Similarly, among the patients in Arm B with G1b infection, an SVR12 was obtained in 22 of 24 patients (91.7%) and in two of three patients (66.7%) with G1a infection (Fig. 4a).

Among patients with an *IL28B* CC genotype, SVR12 rates were 87.5% (21/24) and 95.5% (21/22) in Arms A and B, respectively (Fig. 4b), and among patients with a non-CC *IL28B* genotype, SVR12 was achieved in nine of 10 patients (90.0%) in Arm A and in three of five patients (60.0%) in Arm B.

Table 1 Baseline demographic and disease characteristics

Characteristic	Arm A (Non-cirrhotic) *n* = 34	Arm B (Cirrhotic) *n* = 27
Male gender, *n* (%)	11 (32.4)	17 (63.0)
Mean age ± SD (range), years	49.1 ± 11.7 (22–67)	53.2 ± 8.4 (38–67)
Mean body weight ± SD (range), kg	62.00 ± 12.84 (43.7–91.0)	68.66 ± 11.95 (51.9–105.0)
Mean body mass index ± SD (range), kg/m^2	23.21 ± 3.11 (18.1–29.9)	25.45 ± 2.94 (20.6–33.5)
HCV G1 subtype, *n* (%)	—	—
1a	4 (11.8)	3 (11.1)
1b	30 (88.2)	24 (88.9)
Host *IL28B* genotype (rs12979860), *n* (%)	—	—
CC	24 (70.6)	22 (81.5)
Non-CC	10 (29.4)	5 (18.5)
Mean HCV-RNA level ± SD (range), $\log_{10}$ IU/mL	6.45 ± 0.81 (3.8–7.6)	6.85 ± 0.55 (5.4–7.5)
Patients with fibrosis assessment, *n* (%)	—	—
Liver biopsy	7 (20.6)	1 (3.7)
Noninvasive assessment	30 (88.2)	26 (96.3)
Mean FibroScan® result ± SD (range), kPa[†]	6.26 ± 1.68 (3.3–10.8)	21.18 ± 9.04 (14.5–57.5)
Country of enrollment, *n* (%)	—	—
Korea	10 (29.4)	7 (25.9)
Thailand	7 (20.6)	9 (33.3)
Taiwan	17 (50.0)	11 (40.7)

[†]Cirrhosis is defined as a FibroScan result of ≥ 14.5 kPa. Patients with intermediate readings (9.5−14.4 kPa) were required to have a liver biopsy to confirm the fibrosis score.
HCV, hepatitis C virus; SD, standard deviation.

Among patients with both an *IL28B* CC genotype and G1b infection, identical 95.2% (20/21) SVR12 rates were achieved in Arms A and B (Fig. 4c).

A total of 28 of 61 patients (46%) were enrolled at Taiwanese study sites; among whom, the overall SVR12 rates were 94.1% (16/17) in Arm A and 90.9% (10/11) in Arm B (Table S1). Of note, among Taiwanese patients with both an *IL28B* CC genotype and G1b infection, the SVR12 rates were 100% (13/13) and 90% (9/10) in Arms A and B.

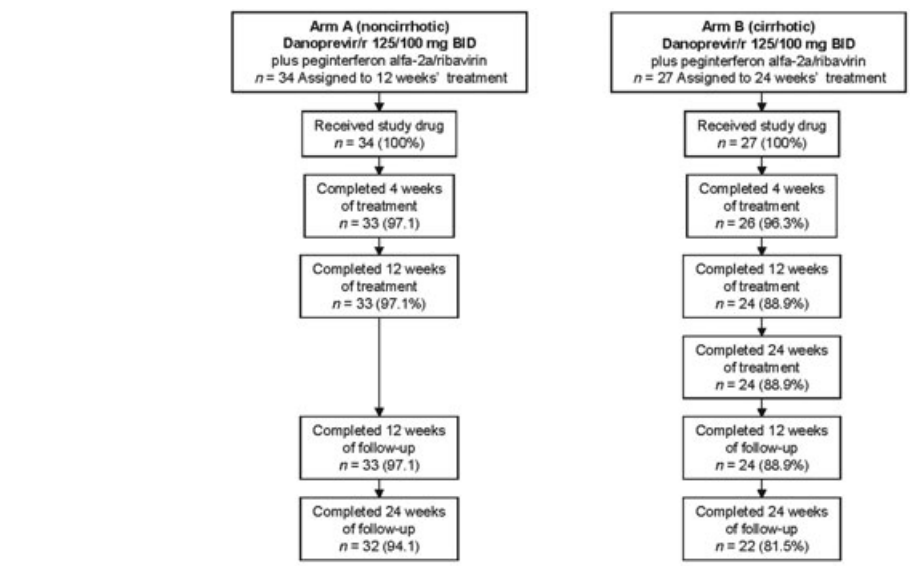
Relapse and viral resistance. Relapse was infrequent and occurred in four patients in Arm A (three G1a, one G1b) and in one patient in Arm B (G1a). Relapse in G1a-infected patients occurred by follow-up Week 4 (two patients with a non-CC *IL28B* genotype) or 12 (two patients with a CC *IL28B* genotype). Danoprevir resistance mutation R155K was detected at the time of relapse; this persisted in all patients until follow-up Week 24.

The G1b patient (Arm A, *IL28B* CC) who relapsed had achieved an SVR12 but had detectable HCV-RNA (201 IU/mL) at follow-up Week 24. When retested 2 months later, the patient was HCV-RNA negative (target not detected). NS3–4A sequence from the virus isolated from the follow-up Week 24 sample did not match that from the baseline sample, with a 10.3% nucleotide difference between the two sequences (and no danoprevir resistance variants). This is consistent with the reported range of nucleotide differences (8% to 12%)[11] between isolates within an HCV subtype obtained from independently infected patients and suggests that the follow-up Week 24 sample may have been inadvertently swapped for another sample or contaminated. The negative follow-up sample also suggests that the isolated positive sample was not attributable to re-infection.

One G1b patient (Arm B, *IL28B* non-CC) experienced viral breakthrough at Week 4, and danoprevir resistance mutation R155K was detected (no follow-up samples were available for further analysis).

Danoprevir resistance mutations were detected in four patients at baseline, one of whom (Arm B, G1a, *IL28B* non-CC with a Q80K mutation) relapsed after an end of treatment response and developed an R155K resistance mutation, whereas the other three (one Q80K, two Q80R) achieved SVR. It has been shown previously that mutations at position 80 confer low-level resistance to danoprevir *in vitro* (less than 10-fold half maximal effective concentration shift).[9,12] No patients had R155K at baseline.

Safety. Danoprevir/r-based triple therapy was well tolerated in noncirrhotic and cirrhotic patients assigned to 12 and 24 weeks of therapy. Most AEs were of mild/moderate severity, and the most common of which were anemia (47.1%), pruritus (35.3%), and neutropenia (32.4%) in Arm A, and anemia (37.0%), neutropenia (29.6%), fatigue (29.6%), and decreased appetite (29.6%) in Arm B (Table 2). Three SAEs (cellulitis, upper respiratory tract infection, and ulnar fracture) were reported in three cirrhotic patients (Arm B), none of which were considered to be related to study drug treatment in the opinion of the investigators. No deaths occurred, and no patients discontinued treatment because of AEs.



Reason for withdrawal from treatment, n (%)		
Adverse events	0	0
Lack of efficacy	0	1 (3.7)
Physician decision	1 (2.9)	0
Withdrawal by patient	0	2 (7.4)
Total	1 (2.9)	3 (7.4)

Figure 2 Patient flow.

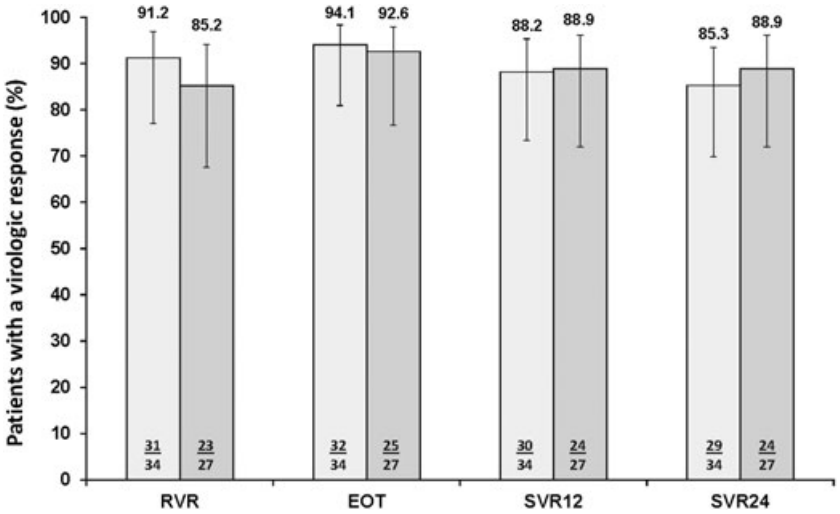


Figure 3 Overall virologic response. Virologic response defined as HCV-RNA below the lower limit of quantitation (25 IU/mL) (Roche COBAS® TaqMan v2.0 HCV Test). EOT, end-of-treatment virologic response; RVR, rapid virologic response (Week 4); SVR, sustained virologic response at 12 weeks (SVR12) or 24 weeks (SVR24) of untreated follow-up. Arm A (noncirrhotic) □, Arm B (cirrhotic) ■.

Grade 3 hemoglobin reductions were reported in five patients in Arm A, and six patients in Arm B and Grade 3 thrombocytopenia were reported in three patients in Arm B (Table 2). No Grade 4 hemoglobin or platelet abnormalities were reported. Grade 3 and 4 neutropenia were reported in similar numbers of patients in Arms A (eight and three, respectively) and B (seven and one, respectively). No Grade 3 or 4 alanine aminotransferase or bilirubin abnormalities were reported.

No patients discontinued any study treatments because of an AE, and no patients experienced an AE that led to interruption of danoprevir/r. Modification of the danoprevir/r dose was not permitted. Nine patients in Arm A (26.5%) and 10 in Arm B (37.0%) experienced an AE leading to modification of the peginterferon dose, most commonly neutropenia (eight patients in each arm). Twelve patients in Arm A (35.3%) and seven in Arm B (25.9%) experienced an AE leading to modification of the RBV dose, most commonly anemia (12 patients in Arm A and seven in arm B)

Pharmacokinetics. One patient (Arm A) was excluded from the pharmacokinetic analysis on Day 1 because of a dosing error and one patient (Arm B) was not included in the pharmacokinetic analysis on Day 14 because of an early withdrawal.

The pharmacokinetic properties of danoprevir were broadly overlapping in cirrhotic (Arm B) and noncirrhotic (Arm A) patients both on Day 1 and at steady state (Day 14) (Table 3). On Day 1, C_{max} occurred between 0.5 and 8 h postdose and was more than twofold higher in Arm B than in Arm A (mean 388 *vs* 174 μg/L). Similarly AUCτ was more than twofold higher in patients in Arm B than in Arm A on Day 1 (mean 1228 *vs* 482 μg • h/L, respectively). The interpatient coefficient of variation (CV) in AUCτ in Arms B and A was 89.3% and 83.5%, respectively.

At steady state (Day 14) exposure to danoprevir was more than twofold higher in Arm B than in Arm A with mean C_{max} values of 378 and 164 μg/L and AUCτ values of 985 and 510 μg • h/L, respectively. The CV in AUCτ in Arms B and A was 89.7% and 87.2%, respectively.

Median trough danoprevir concentrations were similar from Day 3 through 14 and ranged from 5.0 to 10.3 μg/L in Arm B and from 3.0 to 8.0 μg/L in Arm A (Table S2). There was considerable interpatient variability in both groups, with CVs ranging from 81% to 416% in Arm B and from 132% to 389% in Arm A. The highest trough concentrations were observed on Day 3 in both treatment groups.

There was little to no accumulation observed as estimated by mean (SD) AUCτ on Day 14/Day 1 (0.91 [±0 .48] in Arm B and 1.27 [± 0.97] in Arm A).

The mean $t_{1/2}$ of danoprevir was similar in Arms A and B on Day 1 (1.90 *vs* 1.79 h, respectively) and Day 14 (1.56 and 1.48 h, respectively).

Exposure to ritonavir was similar in Arm A and B as indicated by C_{max}, C_{min}, and AUCτ values both on Day 1 and on Day 14 (Table 3 and Table S2).

Discussion

This study demonstrates that the combination of danoprevir/r plus peginterferon alfa-2a/ribavirin results in high virologic response rates and is well tolerated in treatment-naive Asian patients, both with and without cirrhosis. Limitations inherent in the study design include the lack of a control group and the small sample size; in particular, the limited number of patients with G1a infection. However, these results are consistent with placebo-controlled trials in heterogenous patient populations that have shown that SVR rates are generally lower in cirrhotic than noncirrhotic patients and that longer durations of treatment are generally required in cirrhotic than noncirrhotic patients treated with protease inhibitor-based triple therapy regimens. For this reason, the nearly identical SVR12 rates achieved after 12 weeks of treatment in noncirrhotic patients (88.2% in Arm A) and 24 weeks of therapy in cirrhotic patients (88.9% in Arm B) are particularly noteworthy. Among the subgroup of patients with G1b infection, SVR12 rates were 96.7% and 91.7% in Arms A and B, respectively, and among patients with an *IL28B* CC genotype, SVR12 rates were 87.5% and 95.5%, respectively.

Relapse occurred infrequently in the trial but was more common in G1a patients and was consistently associated with the R155K mutation. This pattern is consistent with previous studies that have reported higher rates of relapse in G1a patients in association with

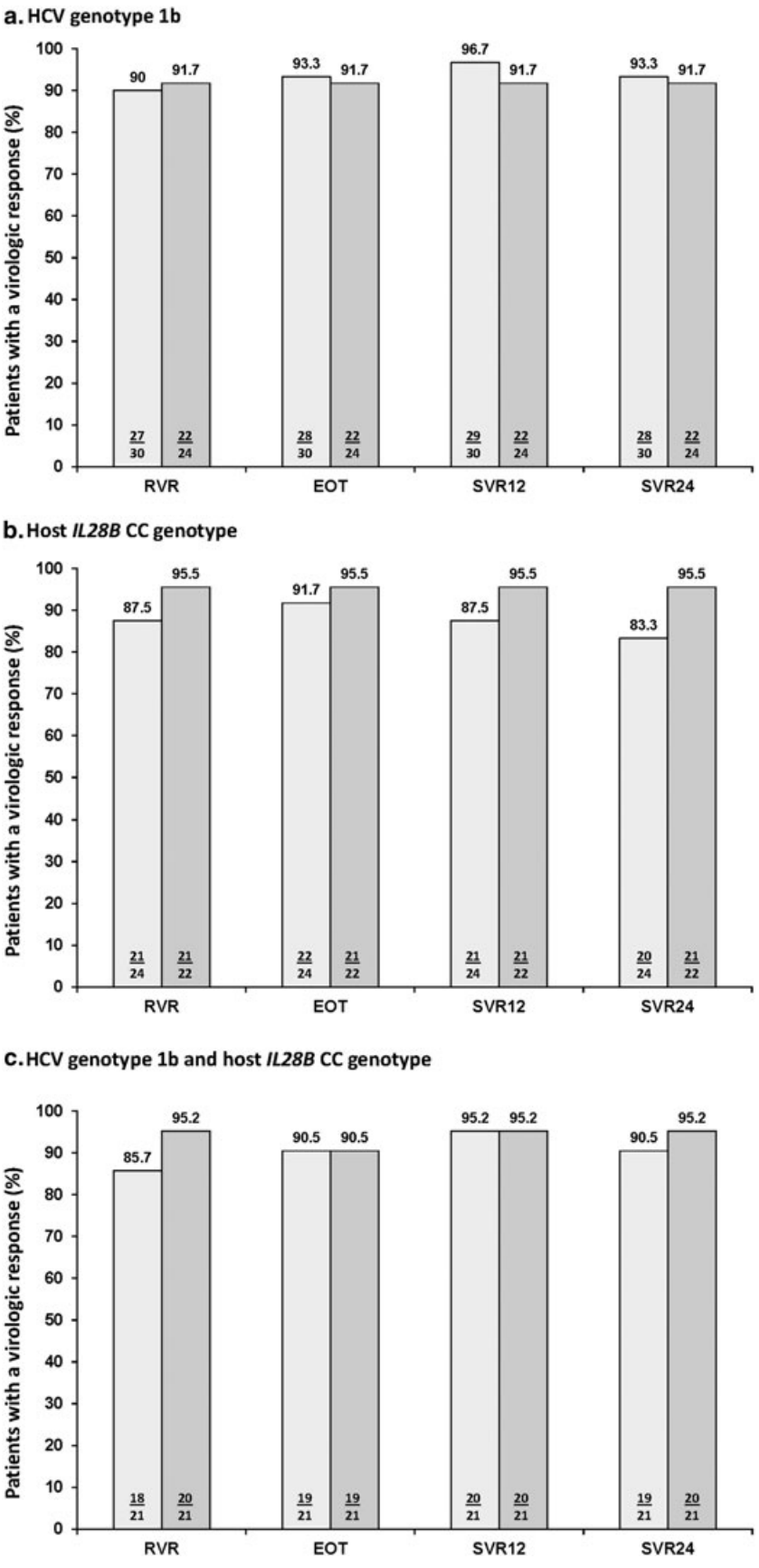


Figure 4 Virologic response in patients with (a) hepatitis C virus (HCV) G1b infection; (b) host *IL28B* CC genotype; (c) both G1b infection and a host *IL28B* CC genotype. Virologic response defined as HCV-RNA below the lower limit of quantitation (25 IU/mL) (Roche COBAS® TaqMan v2.0 HCV Test). EOT, end-of-treatment virologic response; RVR, rapid virologic response (Week 4); SVR, sustained virologic response at 12 weeks (SVR12) or 24 weeks (SVR24) of untreated follow-up. Arm A (noncirrhotic) □, Arm B (cirrhotic) ■.

Table 2 Adverse events and laboratory abnormalities

	Arm A (Noncirrhotic) *n* = 34	Arm B (Cirrhotic) *kn* = 27
Deaths, *n* (%)	0	0
Patients with ≥1 SAE, *n* (%)	0	3 (11.1)[†]
Patients with ≥1 AE, *n* (%)	33 (97.1)	25 (92.6)
Incidence of individual AEs,[‡] *n* (%)	—	—
Anemia[§]	16 (47.1)	10 (37.0)
Pruritus	12 (35.3)	5 (18.5)
Neutropenia	11 (32.4)	8 (29.6)
Headache	10 (29.4)	5 (18.5)
Cough	7 (20.6)	7 (25.9)
Fatigue	7 (20.6)	8 (29.6)
Decreased appetite	5 (14.7)	8 (29.6)
Myalgia	9 (26.5)	6 (22.2)
Alopecia	2 (5.9)	7 (25.9)
Dizziness	8 (23.5)	5 (18.5)
Insomnia	8 (23.5)	6 (22.2)
Diarrhea	8 (23.5)	4 (14.8)
Nausea	8 (23.5)	3 (11.1)
Pyrexia	6 (17.6)	6 (22.2)
Exertional dyspnea	4 (11.8)	6 (22.2)
Thrombocytopenia	1 (2.9)	5 (18.5)
Grade 3 or 4 laboratory abnormalities, *n* (%)	—	—
Hemoglobin	—	—
Grade 3 (< 90–70 g/L)	5 (14.7)	6 (22.2)
Grade 4 (< 70 g/L)	0	0
Neutrophils	—	—
Grade 3 ($< 0.75–0.5 \times 10^9$/L)	8 (23.5)	7 (25.9)
Grade 4 ($< 0.5 \times 10^9$/L)	3 (8.8)	1 (3.7)
Lymphocytes	—	—
Grade 3 ($< 0.5–0.35 \times 10^9$/L)	0	2 (7.4)
Grade 4 ($< 0.35 \times 10^9$/L)	1 (2.9)	1 (3.7)
Platelets	—	—
Grade 3 ($< 50–25 \times 10^9$/L)	0	3 (11.1)
Grade 4 ($< 25 \times 10^9$/L)	0	0

[†]All serious adverse events were considered to be unrelated to study drug in the opinion of the investigators.
[‡]AEs reported in ≥ 15% of patients in either group.
[§]According to investigator's reports, not objective laboratory data.
AE, adverse event; SAE, serious adverse event.

this mutation.[6] The higher barrier to resistance in G1b HCV is attributable to the need for two nucleotide substitutions, rather than one for G1a HCV, to produce the R155K mutation.[13]

Treatment with danoprevir/r-based triple therapy was well tolerated. No treatment-related SAEs were reported, and no patients discontinued treatment in either treatment arm because of AEs. The type and frequency of AEs reported in the trial were typical of those associated with dual-peginterferon alfa-2a/ribavirin therapy,[14–16] and no danoprevir-specific safety signals were observed. Thus, it appears that danoprevir/r does not increase the safety burden of peginterferon alfa-2a/ribavirin in Asian patients with CHC.

There was no control arm in this study, so it is not possible to make direct comparisons with peginterferon/ribavirin dual therapy. However, two previous studies have evaluated 24 and 48 weeks of peginterferon alfa-2a/ribavirin dual therapy in treatment-naïve Asian G1-infected patients.[17,18] The SVR12 rate achieved in the present study in noncirrhotic patients with a CC genotype and G1b HCV infection (87.5%) is somewhat higher than the SVR24 rates achieved after 24 (56–59%) or 48 weeks (76–79%) of dual therapy in the previous studies.[17,18] This indirect comparison serves to highlight a major advantage of danoprevir-based triple therapy, which is a considerably shorter treatment duration than that required with dual therapy. There was a high degree of variability in exposure to danoprevir in both study arms, which may be attributed to presystemic processes including low absolute oral bioavailability (3.9% when administered with ritonavir)[19] and high first-pass hepatic metabolism.[5,10,19–21] Mean exposure to danoprevir was more than twofold higher in patients with well-compensated cirrhosis than in noncirrhotic patients. The difference in exposure observed between cirrhotic and noncirrhotic patients may be the result of lower first-pass metabolism in cirrhotic patients. It is reassuring that the accumulation ratio was < 1 in cirrhotic patients, which demonstrates that the drug is not expected to accumulate in these individuals. Importantly, danoprevir/r has been administered at dosages ranging from 50/100 to 200/100 in combination with peginterferon alfa-2a/ribavirin in a larger study with no evidence of dose-related safety or tolerability issues.[6] There was less variability in the pharmacokinetics of ritonavir, both with respect to variability between both treatment arms and interpatient variability. In contrast to estimates of exposure to danoprevir, ritonavir exposure was somewhat higher in noncirrhotic patients than in cirrhotic patients. This study is the first to evaluate danoprevir-based triple therapy in Asian patients with chronic hepatitis C, and the SVR12 rates are comparable with those obtained with interferon-free and interferon-based DAA-containing regimens in patients with G1b infection.[22–27] Moreover, the 12- and 24-week treatment durations used in noncirrhotic and cirrhotic patients in this study produced efficacy and safety results that are similar to those achieved in previous trials with DAA-containing regimens.[22–27]

Interferon-free combinations of DAAs have recently become available for treatment of HCV G1 infection, with more such regimens likely to gain approval in the near future. International guidelines recommend interferon-free combinations as the preferred treatment for HCV G1 infection.[3,4] Guidelines of the European Association for the Study of the Liver are noteworthy in that they recognize that access to DAAs is not uniform across different geographical regions and, in some countries, interferon-free regimens may be unavailable or unaffordable for many patients, for whom triple therapy with a peginterferon-based regimen may be the best available option.[4]

These results suggest that danoprevir/r-based triple therapy is well suited to the treatment of CHC in Asia, where a majority of patients are infected with G1b and most patients (84%) have an *IL28B* CC genotype.[8] Larger studies are needed to confirm the efficacy and safety of this combination in Asian patients with HCV G1 infection.

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Table 3 Pharmacokinetic parameters for danoprevir and ritonavir on Days 1 and 14 (steady state)

Pharmacokinetic parameter†	Danoprevir				Ritonavir			
	Day 1		Day 14		Day 1		Day 14	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
C_{max}, μg/L	174 (170) [21–760]	388 (318) [87–1380]	164 (121) [19–508]	378 (327) [18–1180]	839 (450) [278–1840]	652 (365) [156–1450]	2170 (871) [796–4080]	1910 (1060) [512–4530]
t_{max}, h	2.96 (1.79) [0.50–8.05]	2.72 (1.00) [0.50–6.00]	2.70 (1.14) [0.53–4.08]	3.13 (1.69) [1.00–8.08]	4.61 (1.92) [1.00–12.05]	4.29 (1.31) [0.50–6.00]	3.94 (1.51) [1.00–8.00]	4.21 (1.41) [2.00–8.08]
C_{min}, μg/L	NA	NA	2.12 (1.71) [0.22–7.63]	4.41 (4.47) [0.61–19.8]	NA	NA	344 (132) [166–725]	343 (216) [108–1110]
AUCτ, μg • h/L	482 (402) [105–1631]	1228 (1096) [307–5212]	510 (435) [70–2110]	985 (883) [100–3823]	4565 (1911) [1599–8146]	3914 (1652) [1088–5982]	12 268 (4234) [5854–21 969]	10 234 (4635) [3470–21 236]
CL/F, L/h	426 (296) [76–1140]	168 (111) [23–390]	479 (416) [59–1793]	212 (168) [33–670]	15 (4) [11–20]	26 (16) [14–58]	9 (3) [5–17]	10 (4) [5–17]
Vz/F, L	1190 (942) [128–3330]	423 (296) [70–1220]	1110 (1070) [118–4790]	469 (434) [69–1620]	78 (24) [33–110]	130 (75) [61–275]	42 (19) [18–85]	50 (16) [27–75]
$t_{½}$,h	1.90 (0.472) [1.15–3.06]	1.79 (0.532) [1.10–3.35]	1.56 (0.397) [1.15–3.35]	1.48 (0.360) [0.87–2.26]	3.53 (0.849) [1.96–4.62]	3.51 (0.359) [2.88–4.14]	3.30 (0.611) [2.27–4.72]	3.57 (0.456) [2.66–4.10]

†All values are means (± SD) [range].

AUCτ, area under the plasma concentration–time curve (AUC) during the dosing interval (τ); C_{max}, maximum observed plasma concentration; C_{min}, trough plasma concentration; CL, total body clearance; F, bioavailability; NA, not applicable; $t_{½}$, elimination half-life; t_{max}, time of observed C_{max}; Vz, total volume of distribution.

Paik, and Junghwan Yoon; Taiwan—Wan-Long Chuang, Shih-Jer Hsu, and Cheng-Yuan Peng; Thailand—Piyawat Komolmit.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Definitions used to select patients for the viral resistance monitoring.
Table S1. Results in patients enrolled at study sites in Taiwan.
Table S2. Trough plasma concentrations (C_{min}) of danoprevir and ritonavir.