CLINICAL TRIALS AND THERAPEUTIC

Simeprevir plus peginterferon/ribavirin for HCV genotype 1-infected treatment-naïve patients in China and South Korea

Lai Wei, * Tao Han, † Dongliang Yang, ‡ Jeong Heo, § Jia Shang, ¶ Jun Cheng, ** Xinyue Chen, †† Qing Xie, †‡ Ju-Hyun Kim, §§ Ronald Kalmeijer, ††† Sivi Ouwerkerk-Mahadevan, *** Eva Hoeben, *** Oliver Lenz, ††† Thierry Verbinnen, ††‡ Rekha Sinha, †‡‡ MengChun Li, §§§ Jane Scott, ¶¶¶ Monika Peeters and †††† James Witek, ††††† on behalf of the TIGER team

*Peking University People’s Hospital, Peking University Hepatology Institute and Peking Key Laboratory for Hepatitis C and Immune Therapy, ††††Beijing Ditan Hospital, †††Beijing You An Hospital, Capital Medical University, †††China R&D and Scientific Affairs, Xi’an Janssen Pharmaceutical Company, Beijing, †Tianjin Third Central Hospital, Tianjin, ‡Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, ‡‡Henan Provincial People’s Hospital, Zhengzhou, ‡‡‡Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; §Pusan National University and Medical Research Institute, Busan, §§Gachon University Gil Medical Center, Incheon, Republic of Korea; †††Janssen Global Services LLC, ††††Janssen Research & Development LLC, Titusville, NJ, USA; ***Janssen Research & Development BVBA, †††††Janssen Pharmaceutica NV, Beerse, Belgium; and †††††Janssen Global Services LLC, High Wycombe, UK

Key words
East Asia, HCV non-structural (NS)3/4A protease inhibitor, hepatitis C virus, simeprevir, sustained virologic response.

Accepted for publication 14 December 2015.

Correspondence
Dr Lai Wei, Peking University People’s Hospital, No 11, Xizhimen South Street, Xicheng District, Beijing 100044, China. Email: weila@pkuph.edu.cn

Conflicts of interest: Lai Wei has been on advisory boards and acted as a consultant for AbbVie, Abbott, BMS, Gilead Sciences, Johnson & Johnson, MSD, Novartis, and Roche; has been a speaker for Abbott, BMS, Gilead Sciences, MSD, Novartis, and Roche; and has grant support from BMS and Roche. Dongliang Yang has been on advisory boards or acted as a consultant for AbbVie, Abbott, BMS, Gilead Sciences, Johnson & Johnson, MSD, Novartis, and Roche; has been a speaker for Abbott, BMS, Gilead Sciences, MSD, Novartis, GSK, and Roche; and has grant support from BMS and Roche. Dongliang Yang has been on advisory boards or acted as a consultant for AbbVie, Abbott, BMS, Gilead Sciences, Johnson & Johnson, MSD, Novartis, GSK, and Roche; has been a speaker for Abbott, BMS, Gilead Sciences, MSD, Novartis, GSK, and Roche. Xinyue Chen has been a speaker for BMS and Roche. Ju-Hyun Kim has acted as a consultant for BMA and Gilead Sciences. Tao Han, Jeong Heo, Jia Shang, Jun Cheng, and Qing Xie have no conflicts of interest. MengChun Li was an employee of Xi’an Janssen Pharmaceutical Company at the time of the study. Ronald Kalmeijer, Sivi Ouwerkerk-Mahadevan, Eva Hoeben, Oliver Lenz, Thierry Verbinnen, Rekha Sinha, Jane Scott, Monika Peeters, and James Witek are employees of Janssen and may be Johnson & Johnson stockholders.

The copyright line for this article was changed on 18 May 2017 after original online publication.

Abstract

Background and Aim Approximately one-third of patients with hepatitis C virus (HCV) genotype (GT) 1 infection live in East Asia. This study evaluated the efficacy, pharmacokinetics, safety, and tolerability of simeprevir plus peginterferon alpha-2a and ribavirin (PR) in HCV GT1-infected, treatment-naïve, Asian patients with compensated liver disease.

Methods This phase III, randomized study (NCT01725529) was conducted in China and South Korea. Patients received simeprevir 150 mg once daily (QD), simeprevir 100 mg QD, or placebo, in combination with PR for 12 weeks. Patients in the simeprevir groups received PR alone for a further 12 or 36 weeks based on response-guided treatment criteria. Patients in the placebo group received a further 36 weeks of PR alone. The primary efficacy endpoint was sustained virologic response 12 weeks after planned end of treatment (SVR12). Secondary endpoints were safety, pharmacokinetics, tolerability, and patient-reported outcomes.

Results Overall, 457 patients were treated; the majority had GT1b infection (452/457 [99%]) and IL28B CC GT (364/457 [80%]). Of the 454 patients who had liver biopsy, 26 had cirrhosis (6%). SVR12 rates were superior for both the simeprevir 100 mg (89%; P < 0.001) and 150 mg (91%; P < 0.001) groups versus placebo (76%). Adverse events were mainly grade 1/2 and occurred at a similar incidence across all treatment groups. Overall, eight patients (2%) discontinued simeprevir or placebo treatment because of adverse events.

Conclusions Both simeprevir (100 mg and 150 mg QD) plus PR achieved superior SVR12 versus placebo plus PR in treatment-naïve, HCV GT1-infected, Asian patients and were well tolerated.
Introduction

Hepatitis C virus (HCV) infection is the leading cause of liver cirrhosis, hepatocellular carcinoma, and liver transplantation worldwide. There are at least six major HCV genotypes (GTs), with the most common being GT1. Of approximately 83.4 million patients with HCV GT1 infection worldwide, around one-third lives in East Asia.

Within HCV GT1, GT1b is the most prevalent subtype in both China and South Korea. The majority of Chinese patients (84%) have the CC polymorphism (based on a single nucleotide polymorphism (SNP) on chromosome 19; rs12979860) in close proximity to the IL28B gene, which has been associated with an increased response to HCV treatment.

Previously, the standard of care for HCV-infected patients with cirrhosis was treatment with peginterferon alpha in combination with ribavirin (RBV) (PR) and the direct-acting antiviral agents boceprevir and telaprevir. However, these direct-acting antivirals are associated with frequent dosing regimens, large pill burdens, and poor tolerability. Furthermore, adverse events (AEs) associated with these agents include rash and anemia.

Simeprevir is an oral, once-daily (QD) non-structural protein (NS)3/4A protease inhibitor with antiviral activity against HCV GTs 1, 2, 4, 5, and 6. Simeprevir is approved in combination with PR for chronic GT1 infection in Japan and other countries, and for GT 1 and 4 infection in the USA and European Union.

Data from a phase I study indicated that in Asian healthy volunteers and patients, simeprevir plasma exposure with a 100 mg dose is similar to that with 150 mg in Caucasians. Based on these data and the simeprevir safety profile from global phase III studies, the current study investigated the efficacy, pharmacokinetics (PK), safety, and tolerability of simeprevir 100 mg QD and 150 mg QD when either was added to PR in treatment-naïve Chinese and South Korean patients with chronic HCV GT1 infection.

Methods

Study design. This phase III, randomized, double-blind, double-dummy, placebo-controlled, three-arm, multicenter study (TIGER; TMC435HPC3005) assessed the efficacy, PK, tolerability, and safety of simeprevir (100 mg or 150 mg) plus PR versus placebo plus PR in treatment-naïve patients with HCV GT1 infection.

The institutional review boards of all participating institutions approved the study. Written informed consent was obtained from all participants according to local regulations.

Patients. Eligibility criteria are provided in the study registration information (NCT01725529). In brief, eligible patients (aged 18–70 years) had confirmed chronic HCV GT1 infection, screening plasma HCV-RNA concentration > 10 000 IU/mL, and no history of treatment for HCV infection. All patients were required to have compensated liver disease. Patients with cirrhosis were eligible if an ultrasound scan within the previous 2 months showed no evidence of hepatocellular carcinoma. Key exclusion criteria included hepatic decompensation (historical or current evidence of ascites, bleeding varices, or hepatic encephalopathy), any liver disease of non-HCV etiology, and co-infection with non-GT1 HCV, HIV-1/HIV-2, or hepatitis B virus (Supporting Information).

Randomization and masking. Patients were randomly assigned in a 1:1:1 ratio to receive simeprevir 100 mg, 150 mg, or placebo and stratified by HCV GT subtype (1a, 1b, or other) and IL28B GT (SNP rs12979860; CC, CT, or TT) (Supporting Information).

Treatment. Patients received simeprevir 100 mg QD, 150 mg QD, or placebo in combination with peginterferon alpha (180 μg/week) and RBV (1000 mg or 1200 mg/day, depending on bodyweight [< 75 kg or ≥ 75 kg, respectively]). Patients in the simeprevir groups received 100 mg or 150 mg in combination with matching placebo and PR for 12 weeks, followed by PR alone for a further 12 or 36 weeks based on response-guided treatment (RGT) criteria. According to RGT criteria, treatment was completed at week 24 if HCV-RNA was < 25 IU/mL detectable or undetectable at week 4 and < 25 IU/mL undetectable at week 12.

Study assessments. To assess the virologic response to treatment, plasma HCV-RNA was quantified at screening and at defined time points thereafter using the COBAS TaqMan HCV/High Pure System assay (version 2.0; Roche, Molecular Diagnostics, Pleasanton, CA, USA; lower limit of quantification 25 IU/mL and limit of detection 15 IU/mL).

Viral sequencing of the HCV NS3/4A protease domain was performed at baseline in all patients and post-baseline in patients not achieving sustained virologic response (SVR) to identify pre-existing polymorphisms and emerging mutations associated with resistance to simeprevir.

Blood samples were collected to allow determination of the plasma concentration of simeprevir and PR as appropriate. AEs were monitored throughout the study and until the end of the follow-up period.

Outcomes. The primary efficacy endpoint was the proportion of patients achieving SVR 12 weeks after planned end of treatment (EOT) (SVR12). Analyses of SVR12 rates according to baseline characteristics were also performed.

Secondary endpoints included SVR 24 weeks after planned EOT (SVR24); on-treatment virologic response; incidences of viral breakthrough, on-treatment failure, and viral relapse; evaluation of the HCV NS3/4A sequence in patients not achieving SVR; and the proportion of patients meeting RGT criteria for 24 weeks of treatment.

The PK of simeprevir was evaluated in this Asian population to determine the relationship between the population-derived exposure parameters and efficacy and safety parameters.
Prespecified secondary safety endpoints included PRO scores for fatigue (Fatigue Severity Scale [FSS])\textsuperscript{13} and depressive symptom severity (Center for Epidemiologic Studies Depression Scale).\textsuperscript{13} Productivity and activity impairment (Work Productivity and Activity Impairment questionnaire for Hepatitis C),\textsuperscript{13} and health-related quality of life (EuroQoL 5-Dimensions questionnaire visual analog scale).\textsuperscript{15} Further secondary endpoints are detailed in the Supporting Information.

**Statistical methods.** Statistical analyses were performed at an overall two-sided 5% significance level. To account for multiple testing, between-treatment comparisons were performed at the two-sided 2.5% significance level. Study sample size was based on SVR24 response, which is also applicable to SVR12 response and was large enough (450 patients, with 150 patients in each group) to demonstrate the superiority of simeprevir versus placebo with 80% power for the proportion of patients achieving SVR12.

Patients’ baseline demographics and disease characteristics were analyzed descriptively. Efficacy analyses (including the primary endpoint SVR12) were performed on the intent-to-treat population using the Cochran–Mantel–Haenszel test adjusted for the stratification factor IL28B GT (CC or non-CC). Additionally, a 97.5% confidence interval (CI) was calculated for the primary endpoint.

An integrated population PK model was used, including data from Japanese and global patients and healthy volunteers, which had previously been developed to predict simeprevir plasma concentration-time profiles (Janssen and qPharmetra data on file).

For the PRO endpoints, statistical testing was prespecified in a closed testing procedure that evaluated treatment differences sequentially.

Statistical analyses were performed using SAS\textsuperscript{®} (version 9.2; SAS Institute Inc., Cary, NC, USA) on all randomized patients who had received ≥1 dose of study medication and were included in the intent-to-treat population. See the Supporting Information for further details.

**Results**

**Study population.** The study was conducted at 27 sites in China and 13 sites in South Korea from 24 October 2012, and was completed on 15 November 2014. Results from the final analysis at week 72 (last study-related visit) are presented. In total, 697 patients were screened of whom 457 (66%) were randomized and received ≥1 dose of study treatment (simeprevir 100 mg, n = 153; simeprevir 150 mg, n = 152; placebo, n = 152; Fig. 2). In total, 416/457 (91%) patients completed the study. Forty-one (9%) patients discontinued the study prematurely. The main reasons for early study discontinuation were withdrawal of consent (n = 34; 7%) and lost to follow-up (n = 4; < 1%) (Fig. 2). Baseline demographics and disease characteristics were well balanced between treatment groups (Table 1). All patients were Asian with the majority originating from China (367/457 [80%]) and the remainder from South Korea (90/457 [20%]). Approximately, half the patients were female (221/457 [48%]) and the median age was 45 years (range 18–68 years). Most patients had IL28B GT CC (364/457 [80%]) and almost all patients (452/457 [99%]) had HCV GT1b infection. Overall, 26 patients (6%) had cirrhosis, and the median baseline HCV-RNA was 6.76 log\textsubscript{10} IU/mL.

**Sustained virologic response.** SVR12 was achieved by a higher proportion of patients in both simeprevir groups versus placebo. Superiority in SVR12 rates was shown for simeprevir 100 mg (136/153 [89%]) and simeprevir 150 mg (138/152 [91%]) versus placebo (115/152 [76%]) (Table 2). The stratum-adjusted differences in SVR12 rates were significantly superior for both simeprevir 100 mg (13% [97.5% CI 4–23%]; P = 0.003) and 150 mg (15% [97.5% CI 6–25%]; P < 0.001) versus placebo. In addition to overall superiority, SVR12 rates were higher for both simeprevir groups versus placebo within all baseline characteristic categories including IL28B GT, METAVIR score, gender, and HCV-RNA concentration. All (5/5) METAVIR F4 patients treated with simeprevir 150 mg achieved SVR12 (Table 2).

The majority of simeprevir-treated patients met RGT criteria and were eligible to stop treatment at week 24 (simeprevir
100 mg, 143/153 [93%]; simeprevir 150 mg, 143/152 [94%]. Of these, 268/286 (94%) simeprevir-treated patients achieved SVR12 (Supporting Information Table S1; Supporting Information).

Virologic response over time. Overall, a higher proportion of patients achieved rapid virologic response (< 25 IU/mL undetectable at week 4) and week 4 HCV-RNA < 25 IU/mL detectable or undetectable in the simeprevir groups versus placebo (Table 2).

Treatment failure. A higher proportion of patients in the placebo group had on-treatment failure versus the simeprevir groups (Table 2), which impacted on the placebo SVR12 rate. All patients with viral breakthrough met a virologic stopping rule. The majority of patients in the simeprevir groups who did not achieve SVR12 (for any reason) had missing data at the SVR12 time point (simeprevir 100 mg, 10/17 [59%] patients; simeprevir 150 mg, 6/14 [43%] patients; placebo, 4/37 [11%] patients).

Viral relapse rates were similar for simeprevir 100 mg and 150 mg, and were lower than those for placebo (Table 2). Viral relapse mostly occurred within the first 12 weeks after EOT (simeprevir 100 mg, 2/2 patients; simeprevir 150 mg, 3/4 patients; placebo, 14/15 patients).

NS3 sequencing analysis. Baseline amino acid polymorphisms at NS3 positions that are known to reduce simeprevir in vitro activity16 (simeprevir fold change in 50% effective concentration > 2.0) were observed in 15/453 (3%) patients with baseline sequence information available and were located at NS3 positions 80 (Q80H; K; R), 168 (D168E), or 170 (V170T). The NS3 Q80K polymorphism was only present at baseline in 2/453 (< 1%) patients (both infected with HCV GT1b). In total, 8/15 (53%) patients with baseline polymorphisms were enrolled in the simeprevir groups, and 7/8 (88%) achieved SVR12, including the two patients with Q80K. The one patient who did not achieve SVR12 had Q80R at baseline and was categorized as ‘failure due to missing data’ at the SVR12 time point after having achieved undetectable HCV-RNA at EOT.

Of the patients with NS3 sequencing data available who did not achieve SVR, 6/6 (100%) and 4/7 (57%) in the simeprevir 100 mg and 150 mg groups, respectively, had emerging mutations. These were at position D168V in all patients except one (simeprevir 150 mg group) who had a Q80R mutation in combination with a D168E mutation.

Pharmacokinetics. Simeprevir exposure increased more than dose-proportionally. Population PK analyses showed a 2.8-fold higher geometric mean exposure (area under the plasma concentration-time curve [AUC24h]) for simeprevir 150 mg versus 100 mg. Mean simeprevir AUC24h was 44 606 ng · h/mL and 123 324 ng · h/mL, respectively, for the 100 mg and 150 mg doses (Supporting Information Table S2). See Supporting Information for further details.

An exposure-related increase in the AE of increased bilirubin was seen, although this increase did not indicate liver toxicity.
Overall, the proportions of patients experiencing any AE, grade 3/4 AEs, and serious AEs (SAEs) were similar across treatment groups (Table 3). Most AEs occurring during the first 12 weeks and the entire treatment phase were grade 1/2 in severity. Permanent discontinuation of simeprevir due to an AE occurred in a similar proportion of patients in the simeprevir 100 mg (three patients, 2%) and 150 mg (four patients, 3%) groups. AEs led to the discontinuation of placebo in one patient (1%).

The most commonly reported AEs (>20% of patients) were similar across treatment groups with the exception of AEs related to increased bilirubin, which were more common in the combined simeprevir groups during the first 12 weeks and entire treatment phase.

The incidence of SAEs was low in the first 12 weeks (simeprevir 100 mg, one patient [1%]; simeprevir 150 mg, two patients [1%]; placebo, one patient [1%]); none were considered related to treatment.

Among the AEs of special/clinical interest during the first 12 weeks, the incidence of rash (any type) was approximately 17% for both simeprevir groups and 13% for placebo. Rash led to permanent discontinuation of simeprevir 100 mg in one patient and of 150 mg in two patients. No grade 4 rash or rash SAEs were reported. Photosensitivity was reported in one patient (1%) in each simeprevir group; in the 150 mg group, grade 3 photosensitivity led to discontinuation of treatment. The incidence of increased bilirubin was higher with simeprevir 150 mg (44%) versus simeprevir 100 mg (29%) and placebo (18%), and led to discontinuation in one patient in the simeprevir 150 mg group. The majority of these events were grade 1/2, not associated with increases in liver transaminases and were reversible on completion of simeprevir. No relevant differences in grade 3 AEs were observed between the simeprevir groups. Similarly, no clinically relevant differences were seen for pruritus, anemia, neutropenia, dyspnea, or upper gastrointestinal events (Supporting Information Table S3).

Changes in laboratory parameters are detailed in the Supporting Information. Up to week 24, no clinically significant differences in

### Table 1  Baseline demographics and disease characteristics (ITT population)

| Country, n (%) | Simeprevir 100 mg plus PR (n = 153) | Simeprevir 150 mg plus PR (n = 152) | Placebo plus PR (n = 152) |
|----------------|-------------------------------------|------------------------------------|---------------------------|
| China 122 (80) | 123 (81)                            | 122 (80)                           |
| South Korea 31 (20) | 29 (19)                            | 30 (20)                           |
| Female 67 (44) | 75 (49)                             | 79 (52)                           |
| Age (years), median (range) | 45.0 (18.0–68.0) | 44.0 (19.0–68.0) | 45.0 (18.0–68.0) |
| IL28B genotype, n (%) | CC 123 (80) | CT 29 (19) | TT 1 (1) |
| Baseline HCV-RNA (log10 IU/mL), median (range) | 6 (4.5–7.9) | 6 (1.4–7.5) | 6.7 (3.8–7.6) |

| METAVIR fibrosis score, n/N (%) | F0–F1/S0–S1 87/153 (57) | F2/S2 39/153 (25) | F3/S3 18/153 (12) | F4/S4 9/153 (6) |
|--------------------------------|-------------------------|------------------|------------------|------------------|
| HCV genotype, n (%) | 1a 2 (1) | 1 (1) | 2 (1) |
| 1b 151 (99) | 151 (99) | 150 (99) |
| FSS score, mean (SE)³ | 3.4 (0.1) | 3.5 (0.1) | 3.3 (0.1) |
| CES-D score, mean (SE)⁴ | 10.0 (0.7) | 11.7 (0.8) | 9.3 (0.6) |
| WPAI daily activity impairment score, mean (SE)** | 14.1 (1.5) | 19.9 (2.0) | 14.8 (1.7) |
| WPAI productivity impairment score, mean (SE)** | 15.5 (1.6) | 21.4 (2.1) | 15.9 (1.7) |
| EQ-5D VAS score, mean (SE)** | 87.6 (1.0) | 87.4 (1.0) | 87.6 (1.0) |

³Based on a single nucleotide polymorphism on chromosome 19, rs12979860.

⁴Available for patients who had a liver biopsy within 3 years before informed consent or during the screening period with histology consistent with chronic HCV infection. In the Chinese subgroup, the score (S0–S4) was based on the Chinese guideline and is equivalent to METAVIR score (F0–F4).

⁵Normal reference value 2.3; range 1–7.

⁶Normal reference value 16 (lower threshold for depression); range 0–60.

**Normal reference value not available; range 0–100.

CES-D, Center for Epidemiologic Studies Depression Scale; EQ-5D, EuroQol 5-Dimensions questionnaire; FSS, Fatigue Severity Scale; HCV, hepatitis C virus; ITT, intent-to-treat; PR, peginterferon and ribavirin; SE, standard error; VAS, visual analog scale; WPAI, Work Productivity and Activity Impairment questionnaire for Hepatitis C.

**Safety.** Overall, the proportions of patients experiencing any AE, grade 3/4 AEs, and serious AEs (SAEs) were similar across treatment groups (Table 3). Most AEs occurring during the first 12 weeks and the entire treatment phase were grade 1/2 in severity. Permanent discontinuation of simeprevir due to an AE occurred in a similar proportion of patients in the simeprevir 100 mg (three patients, 2%) and 150 mg (four patients, 3%) groups. AEs led to the discontinuation of placebo in one patient (1%).
hemoglobin values were seen between groups. Mild transient increases in bilirubin were noted in the simeprevir groups during the first 12 weeks of treatment, but were reversible after week 16 of treatment. No clinically significant differences were seen for any other laboratory parameters (Supporting Information Fig. S1).

**Patient-reported outcomes.** The proportion of patients with clinically important improvement (>0.6 decrease) in FSS score was comparable in all treatment groups up to week 24. After that, a higher proportion of patients in the simeprevir groups experienced a clinically important improvement in FSS score versus placebo. Clinically important (≥0.5) differences were observed between the combined simeprevir groups and placebo at weeks 36 and 48. At weeks 60 and 72, there was a clinically important improvement from baseline (>0.5 decrease) in the simeprevir/PR groups (Supporting Information Fig. S2a). A statistically significant difference in FSS area under the curve from baseline to week 72 (AUC72) was observed between the simeprevir 100 mg and placebo groups; however, the difference for simeprevir 150 mg versus placebo was not statistically significant (Supporting Information Table S4). Results for other PRO measures are detailed in the Supporting Information.

**Discussion.** The primary objective of the phase III TIGER study was met as both simeprevir 100 mg and 150 mg showed superiority in SVR12 rates versus placebo. Superiority in SVR12 rates was also seen within baseline characteristic categories including IL28B GT and METAVIR score for simeprevir versus placebo. Notably, all five METAVIR F4 patients treated with simeprevir 150 mg achieved SVR12. For both simeprevir groups, rates of on-treatment failure, viral breakthrough, and viral relapse were similar and lower than those for placebo, which impacted on SVR12 rates. Furthermore, RGT criteria were met by the majority of patients treated with simeprevir 100 mg and 150 mg (93% and 94%, respectively), enabling treatment to be stopped at week 24. This was supported by the high SVR12 rate of 94% achieved by these patients.

The results of the current study are in agreement with those from a real-world study in Japanese HCV GT1b-infected patients, which reported an SVR12 rate of 85% for simeprevir plus PR and concluded that simeprevir plus PR continues to be a useful treatment option in Japanese patients.17

---

### Table 2 Primary and key secondary endpoints (ITT population)

| Endpoint                           | Simeprevir 100 mg plus PR | Simeprevir 150 mg plus PR | Placebo plus PR |
|------------------------------------|----------------------------|---------------------------|-----------------|
| Primary endpoint: SVR12†           | 136/153 (89)               | 138/152 (91)              | 115/152 (76)    |
| METAVIR F0–F2/S0–S2‡               | 112/126 (89)               | 115/127 (91)              | 98/121 (81)     |
| METAVIR F3/S3‡                    | 17/18 (94)                 | 17/18 (94)                | 11/18 (61)      |
| METAVIR F4/S4‡                    | 7/9 (78)                   | 5/5 (100)                 | 6/12 (50)       |
| IL28B CC§                         | 107/123 (87)               | 112/119 (94)              | 96/122 (79)     |
| IL28B non-CC‡                     | 29/30 (97)                 | 26/33 (79)                | 19/30 (63)      |
| Male                               | 75/86 (87)                 | 67/77 (87)                | 56/73 (77)      |
| Female                             | 61/67 (91)                 | 71/75 (95)                | 59/79 (75)      |
| Baseline HCV-RNA ≤80000 IU/mL     | 23/25 (92)                 | 24/24 (100)               | 24/26 (92)      |
| Baseline HCV-RNA >80000 IU/mL     | 113/128 (88)               | 114/128 (89)              | 91/126 (72)     |
| SVR24                              | 136/153 (89)               | 138/152 (91)              | 114/152 (75)    |
| RVR‡                               | 136/152 (89)               | 132/150 (88)              | 29/152 (19)     |
| Week 4 HCV-RNA <25 IU/mL (detectable and undetectable) | 148/152 (97)               | 147/150 (98)              | 59/152 (39)     |
| On-treatment failure***            | 5/153 (3)                  | 5/152 (3)                 | 19/152 (13)     |
| Viral breakthrough****             | 4/153 (3)                  | 4/151 (3)                 | 3/152 (2)       |
| Viral relapse**                   | 2/142 (1)                  | 4/141 (3)                 | 15/131 (11)     |

All data are n/N (%).
†HCV-RNA < 25 IU/mL undetectable at EOT and < 25 IU/mL detectable or undetectable 12 weeks after planned EOT. Missing at SVR12 time point: simeprevir 100 mg, 10/153 (7%); simeprevir 150 mg, 6/152 (4%); placebo, 4/152 (3%).
‡In the Chinese subgroup, the score (S0–S4) was based on the Chinese guideline and is equivalent to METAVIR score (F0–F4).
§Based on a single nucleotide polymorphism on chromosome 19, rs12979860.
¶§HCV-RNA based on a single nucleotide polymorphism on chromosome 19, rs12979860.
**HCV-RNA ≤100 IU/mL in patients who had previously achieved <25 IU/mL while on study treatment.
***HCV-RNA ≥1.0 log10 increase in HCV-RNA from the lowest level reached, or confirmed HCV-RNA > 100 IU/mL in patients who had previously achieved <25 IU/mL undetectable at actual EOT.
****>0.5 decrease) in FSS area under the curve from baseline to week 72 (AUC72) was observed between the simeprevir 100 mg and placebo groups; however, the difference for simeprevir 150 mg versus placebo was not statistically significant (Supporting Information Table S4). Results for other PRO measures are detailed in the Supporting Information.
Baseline NS3 Q80K polymorphisms in this study were rare as almost all patients were infected with HCV GT1b. Emerging mutations at the time of treatment failure were mainly D168V, which is commonly observed at treatment failure with simeprevir plus PR therapy in patients infected with HCV GT1b. This finding is in agreement with those of the global phase III simeprevir studies.

The PK of simeprevir was also investigated in the current study. Plasma exposure with simeprevir 100 mg in Asian patients was similar to that seen with 150 mg in non-Asian patients in the global phase III studies, while plasma exposure with simeprevir 150 mg was 2.1-fold higher in this study versus the global phase III studies.

### Table 3  Summary of AEs during the first 12 weeks of treatment and the entire treatment phase (ITT population)

| AE                                      | First 12 weeks | Entire treatment phase |
|-----------------------------------------|----------------|------------------------|
|                                         | Simeprevir     | Placebo                |
|                                         | 100 mg plus PR | PR (n = 153)           |
|                                         | 150 mg plus PR | PR (n = 152)           |
|                                         | Placebo plus PR| PR (n = 152)           |
| Any AE                                  | 146 (95)       | 147 (97)               |
| Grade 1/2 AE                            | 102 (67)       | 96 (63)                |
| Grade 3 AE                              | 35 (23)        | 40 (26)                |
| Grade 4 AE                              | 9 (6)          | 11 (7)                 |
| Grade 3/4 AE possibly related to simeprevir/placebo | 5 (3) | 9 (6) | 2 (1) |
| SAE                                     | 1 (1)          | 2 (1)                  |
| AE with fatal outcome                   | 0              | 0                      |
| AE leading to permanent discontinuation of simeprevir/placebo† | 3 (2) | 4 (3) | 1 (1) |
| AE leading to permanent discontinuation of all study drugs | 2 (1) | 2 (1) | 1 (1) |
| Most common AEs by reported term (>20% of patients) | | | |
| Neutrophil count decreased               | 79 (52)        | 80 (53)                |
| White blood cell count decreased         | 69 (45)        | 79 (52)                |
| Platelet count decreased                 | 46 (30)        | 61 (40)                |
| Blood bilirubin increased               | 31 (20)        | 54 (36)                |
| Hemoglobin decreased                    | 32 (21)        | 34 (22)                |
| Bilirubin conjugated increased           | 10 (7)         | 33 (22)                |
| Pyrexia                                 | 28 (18)        | 38 (25)                |
| Fatigue                                 | 33 (22)        | 24 (16)                |
| Anemia                                  | 27 (18)        | 36 (24)                |
| AEs of special interest                 |                |                        |
| Increased bilirubin                     | 45 (29)        | 67 (44)                |
| AEs of clinical interest                |                |                        |
| Rash (any type)                         | 25 (16)        | 27 (18)                |
| Pruritus                                | 20 (13)        | 14 (9)                 |
| Photosensitivity conditions              | 1 (1)          | 1 (1)                  |
| Neutropenia                             | 104 (68)       | 106 (70)               |
| Anemia                                  | 58 (38)        | 68 (45)                |
| Dyspnea                                 | 2 (1)          | 1 (1)                  |
| Upper gastrointestinal tract             | 17 (11)        | 14 (9)                 |

All data are n (%).

†Without regard to PR.

AE, adverse event; ITT, intent-to-treat; PR, peginterferon and ribavirin; SAE, serious adverse event.

The higher simeprevir exposure observed in Asian patients may be explained by a number of hypotheses. Simeprevir is mainly distributed to the liver, and the uptake transporter organic anion-transporting polypeptide (OATP)1B1 plays an important role in the process. Notably, OATP1B1 hepatic uptake transporter expression levels are lower in Japanese patients compared with Caucasians. Furthermore, evidence suggests that Chinese populations have smaller liver volumes compared with Caucasian populations.

Despite the higher drug exposure observed in the simeprevir 150 mg group, simeprevir was well tolerated in this patient population. Higher rates of rash and photosensitivity were not reported in this study. A similar number of AEs were reported in each treatment group.
with the majority being grade 1/2. The most commonly reported AEs in this study (> 20% of patients) are known side effects of PR. There were also few treatment discontinuations due to AEs, and the incidence was similar in both simeprevir treatment groups. Despite the expected greater increase in bilirubin concentrations seen in the simeprevir 150 mg group versus the 100 mg group and placebo, these elevations were transient, not associated with increases in liver enzymes, reversible upon completion of simeprevir, and infrequently led to treatment discontinuation (one patient in the simeprevir 150 mg group).

PRO measures showed that the duration of treatment-related symptoms and impairments was reduced by the addition of simeprevir to PR. FSS results showed that the addition of simeprevir 100 mg or 150 mg to PR did not increase treatment-associated fatigue beyond that observed with PR alone. This finding is consistent with PRO results from all phase Ib studies and phase III simeprevir studies where FSS was assessed.

The strengths of this study include the randomized, placebo-controlled, PR-controlled, study design, and the large number of patients enrolled. A potential limitation of the study was the inclusion of only treatment-naïve patients. A further limitation was that the proportions of patients with HCV GT1a infection and IL28B non-CC GT were small as they were reflective of the population in East Asia. The proportion of META VIR F3/F4 patients was also small. In addition, the study population may not be fully representative of the Asian population as only Chinese and South Korean patients were enrolled.

This study in treatment-naïve Asian patients with chronic HCV GT1 infection living in China and South Korea demonstrated that simeprevir at doses of 100 mg QD and 150 mg QD is superior to placebo with regard to SVR rates. In the larger subgroups, a trend toward better efficacy with the simeprevir 150 mg dose was observed. Additionally, despite the higher drug exposure seen with simeprevir 150 mg, the safety profiles of the two doses were similar. Furthermore, to maximize benefit, including in more difficult-to-treat patients, simeprevir 150 mg QD may provide a therapeutic advantage as the highest tolerated dose.

Acknowledgments
This study (TIGER; ClinicalTrials.gov Identifier: NCT01725529) was funded by Janssen Research and Development. We would like to thank all patients who participated in this study and their families. The authors would also like to thank Michael Lee, Anne Brochot, and Anders Viberg from qPharmetra, Sweden, for their contributions to the data analysis of this study, and the team who conducted the generic ribavirin selection for the China subgroup. Medical writing assistance was provided by Kimberley Haines of Complete Medical Communications and funded by Janssen Global Services, LLC.

References
1 World Health Organization. Hepatitis C—Fact Sheet 164. 2014. Cited 5 May 2015. Available from URL: http://www.who.int/mediacentre/factsheets/fs164/en/.

2 Messina JP, Humphreys I, Flaxman A et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015; 61: 77–87.
3 Wei L, Lok AS. Impact of new hepatitis C treatments in different regions of the world. Gastroenterology 2014; 146: 1145–50.
4 Rao H, Wei L, Lopez-Talavera JC et al. Distribution and clinical correlates of viral and host genotypes in Chinese patients with chronic hepatitis C virus infection. J. Gastroenterol. Hepatol. 2014; 29: 545–53.
5 Cui Y, Jia J. Update on epidemiology of hepatitis B and C in China. J. Gastroenterol. Hepatol. 2013; 28 (Suppl 1): 7–10.
6 Murakawa M, Asahina Y, Nakagawa M et al. Impaired induction of IL28B and expression of IFN lambda4 associated with non-response to interferon-based therapy in chronic hepatitis C. J. Gastroenterol. Hepatol. 2015; 30: 1075–84.
7 Kiser JJ, Flexner C. Direct-acting antiviral agents for hepatitis C virus infection. Annu. Rev. Pharmacol. Toxicol. 2013; 53: 427–49.
8 Butt AA, Yan P, Shaikh OS et al. Virologic response and haematologic toxicity of boceprevir- and telaprevir-containing regimens in actual clinical settings. J. Viral Hepat. 2015; 22: 691–700.
9 Sitole M, Silva M, Spooner L, Comee MK, Malloy M. Telaprevir versus boceprevir in chronic hepatitis C: a meta-analysis of data from phase II and III trials. Clin. Ther. 2013; 35: 190–7.
10 Janssen Research & Development. Olysio™ (simeprevir) US Prescribing Information. 2015. Cited 27 May 2015. Available from URL: http://www.elysio.com/shared/product/olysio/prescribing-information.pdf.
11 Koletzki D, Pattery T, Ferey B, Vanhoren L, Stuyver LJ. Amplification and sequencing of the hepatitis C virus NS3/4A protease and the NS5B polymerase regions for genotypic resistance detection of clinical isolates of subtypes 1a and 1b. Methods Mol. Biol. 2013; 1030: 137–49.
12 Kleinman L, Mannix S, Yuan Y, Kummer S, L’Italien G, Revicki D. Review of patient-reported outcome measures in chronic hepatitis C. Health Qual. Life Outcomes 2012; 10: 92.
13 Radloff LS. A self-report depression scale for research in the general population. Appl. Psychol. Meas. 1977; 1: 385–401.
14 Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993; 4: 353–65.
15 The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 1990; 16: 199–208.
16 Verbinnen T, Ferey B, Vigen L, Jacobs T, De Meyer S, Lenz O. In vitro activity of simeprevir against hepatitis C virus genotype-1 clinical isolates and its correlation with NS3 sequence and site-directed mutants. Antimicrob. Agents Chemother. 2015; 59: 7548–57.
17 Ogawa E, Furusyo N, Kajiwara E et al. Comparative effectiveness and safety study of triple therapy with simeprevir or telaprevir for non-cirrhotic patients with chronic hepatitis C virus genotype 1b infection. J. Gastroenterol. Hepatol. 2015; 30: 1759–67.
18 Lenz O, Verbinnen T, Ferey B et al. Virologic analyses of HCV isolates from genotype 1-infected patients treated with simeprevir plus peginterferon/ribavirin in Phase IIb/III studies. J. Hepatol. 2015; 62: 1008–14.
19 Forns X, Lawitz E, Zeuzem S et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. Gastroenterology 2014; 146: 1669–79.
20 Jacobson IM, Dore DJ, Foster GR et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2014; 384: 403–13.
Simeprevir in Asian patients

21 Manns M, Marcellin P, Poordad F et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2014; 384: 414–26.

22 Tomita Y, Maeda K, Sugiyama Y. Ethnic variability in the plasma exposures of OATP1B1 substrates such as HMG-CoA reductase inhibitors: a kinetic consideration of its mechanism. Clin. Pharmacol. Ther. 2013; 94: 37–51.

23 Barter ZE, Tucker GT, Rowland-Yeo K. Differences in cytochrome p450-mediated pharmacokinetics between chinese and caucasian populations predicted by mechanistic physiologically based pharmacokinetic modelling. Clin. Pharmacokinet. 2013; 52: 1085–100.

24 Scott J, Rosa K, Fu M et al. Fatigue during treatment for hepatitis C virus: results of self-reported fatigue severity in two Phase IIb studies of simeprevir treatment in patients with hepatitis C virus genotype 1 infection. BMC Infect. Dis. 2014; 14: 465.

25 Scott J, Gilles L, Fu M et al. Simeprevir added to peginterferon and ribavirin lessens time with fatigue, depressive symptoms and functional limitations in patients with chronic hepatitis C compared with peginterferon and ribavirin: results from 1161 patients in the QUEST-1, QUEST-2 and PROMISE studies. J. Viral Hepat. 2015; 22: 639–50.

Supporting information

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

Figure S1 Changes in (A) hemoglobin and (B) total bilirubin over the 72-week study period (ITT population).

Figure S2 Patient-reported outcomes over the 72-week study period (ITT population): (a) Fatigue (FSS); (b) Depressive symptom severity (CES-D); (c) Activity impairment (WPAI: Hepatitis C); (c) Productivity impairment (WPAI: Hepatitis C); and (d) Health-related quality of life (EQ-5D VAS).

Table S1 Patients meeting RGT criteria in the simeprevir groups and the corresponding SVR12 (ITT population).

Table S2 Summary of simeprevir exposure measures (ITT population).

Table S3 Incidence and severity of AEs of special and clinical interest (ITT population).

Table S4 Statistical analysis of treatment differences in patient-reported outcome measures (ITT population).