CLINICAL TRIALS AND THERAPEUTIC

Sofosbuvir plus ribavirin with or without peginterferon for the treatment of hepatitis C virus: Results from a phase 3b study in China

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Abstract

Background and Aim: Sofosbuvir is a nucleotide analog inhibitor of the hepatitis C virus (HCV) NS5B RNA polymerase with pan-genotypic potency. This phase 3b study evaluated the safety and efficacy of sofosbuvir + ribavirin ± peginterferon in Chinese patients infected with HCV genotype 1, 2, 3, or 6.

Methods: Patients with genotype 1 or 6 received sofosbuvir + peginterferon/ribavirin for 12 weeks or sofosbuvir + ribavirin for 24 weeks, depending on prior treatment and interferon eligibility. Patients with genotype 2 or 3 received sofosbuvir + ribavirin for 12 or 24 weeks, respectively. The primary endpoint was sustained virologic response at 12 weeks after the end of treatment (SVR12).

Results: Of 389 patients, 42% had genotype 1, 16% genotype 2, 32% genotype 3, and 9% genotype 6. Half were male, 58% were treatment-naïve, and 15% had cirrhosis. SVR12 rates for patients receiving 12 weeks of sofosbuvir + peginterferon/ribavirin were 94% (95% confidence interval [CI], 87–98%) for HCV genotype 1 and 97% (95% CI, 84–100%) for genotype 6. SVR12 rates for those receiving sofosbuvir + ribavirin for 24 weeks were 95% (95% CI, 87–99%) for genotype 1, 100% (95% CI, 40–100%) for genotype 6, and 95% (95% CI, 90–98%) for genotype 3. For genotype 2 patients receiving sofosbuvir + ribavirin for 12 weeks, the SVR12 rate was 92% (95% CI, 83–97%). Twenty patients (5%) relapsed. Ten (3%) experienced serious adverse events. Three (< 1%) discontinued treatment because of adverse events, of whom one died because of treatment-unrelated adverse events.

Conclusions: Sofosbuvir-based regimens were highly effective and safe in Chinese patients with HCV genotype 1, 2, 3, or 6, suggesting sofosbuvir could serve as the backbone for HCV treatment in China irrespective of genotype.

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**Introduction**

Chronic hepatitis C virus (HCV) infection represents a significant medical burden in the People’s Republic of China, where it is the fourth most common infectious disease. Estimates of the prevalence of chronic HCV infection in China range from 0.4% to 1%. The predominant strain of HCV is genotype 1, accounting for approximately 57% of all infections, followed by genotypes 2, 3, and 6, with approximate prevalences of 24%, 9%, and 6%, respectively.

The only currently reimbursed treatment for HCV infection in China is peginterferon plus ribavirin. Despite the high prevalence of the favorable host genotype IL28B CC in China, sustained virologic response (SVR) rates in patients treated with peginterferon and ribavirin are suboptimal, ranging from 55% in patients with HCV genotype 1 to 90% in those with HCV genotype 2 or 3. Moreover, this regimen is contraindicated in many patients and is associated with poor tolerability, especially in patients with advanced liver disease and in older patients.

This is of particular concern in China where the population is rapidly aging and many patients present with advanced liver disease at the time of diagnosis. Treatment duration in China is often longer than elsewhere due to the common use of interferon-based maintenance therapy in non-respondent patients.

There is a clear medical need for more effective and better tolerated regimens.

Sofosbuvir (Gilead Sciences Inc, Foster City, CA) is a nucleotide inhibitor of the HCV NS5B polymerase. Following successful phase 3 trials, sofosbuvir has been approved in combination with ribavirin with and without interferon for the treatment of HCV genotypes 1–6 in Europe, genotypes 1–4 in the USA and Canada, and genotype 2 in Japan.

This phase 3b study assessed the safety and efficacy of sofosbuvir plus ribavirin (with or without peginterferon) for 12 or 24 weeks in treatment-naive and treatment-experienced Chinese patients with chronic HCV genotype 1, 2, 3, or 6 infection.

**Methods**

**Patients.** This study enrolled patients aged ≥ 18 years chronically infected with HCV genotype 1, 2, 3, or 6 and HCV-RNA levels ≥ 10^5 IU/mL. Patients were either treatment-naive or treatment-experienced (failed prior interferon-based therapy and categorized as interferon-intolerant, non-responder, or relapser).

Up to 20% of patients could have compensated cirrhosis as determined by a liver biopsy (Metavir score = 4 or Ishak score ≥ 5) or Fibroscan > 12.5 kPa (FibroScan; Echosens, Paris, France). Patients who had prior exposure to a direct-acting antiviral agent targeting the NS5B polymerase or with contraindications to ribavirin therapy were excluded. Detailed inclusion and exclusion criteria are presented in the Supporting Information.

**Study design and treatment.** In this multicenter, open-label phase 3b study (ClinicalTrials.gov NCT02021643), patients received one of three treatments depending on HCV genotype, previous HCV treatment, and interferon eligibility/tolerance. Patients with HCV genotype 1 or 6 who were treatment-naive/interferon-eligible or treatment-experienced/interferon-tolerant received sofosbuvir plus peginterferon/ribavirin (both Roche Laboratories Inc., Nutley, NJ) for 12 weeks. Patients with HCV genotype 1 or 6 who were treatment-naive/interferon-ineligible or treatment-experienced/interferon-intolerant—and all those with HCV genotype 3—received sofosbuvir plus ribavirin for 24 weeks. All genotype 2 patients received sofosbuvir plus ribavirin for 12 weeks. Sofosbuvir (400 mg) was administered orally as a single tablet once daily, in the morning with ribavirin and food. Ribavirin was administered orally at a dose of 1000–1200 mg (1000 mg for patients weighing < 75 kg and 1200 mg for patients weighing ≥ 75 kg) in a divided daily dose (morning and evening). Peginterferon (180 μg) was self-administered by subcutaneous injection once weekly. Dose reductions and discontinuation of ribavirin and peginterferon were allowed in accordance with product labels.

This study was approved by an independent ethics committee at all participating sites and was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all patients.
primary safety endpoint was any adverse event (AE) leading to permanent discontinuation of study drug(s).

Secondary endpoints included the proportion of patients with HCV-RNA < LLOQ at 4 weeks post-treatment (SVR4), viral breakthrough, and relapse. Viral breakthrough was defined as HCV-RNA ≥ LLOQ after having HCV-RNA < LLOQ on-treatment. Relapse was defined as HCV-RNA ≥ LLOQ during the post-treatment period in patients who achieved HCV-RNA < LLOQ at end of treatment.

Exploratory evaluations included the evaluation of the pharmacokinetic profile of sofosbuvir and its metabolite GS-331007, the impact of baseline characteristics and baseline NS5B resistance-associated substitutions (RASs) on SVR12, and the emergence of NS5B RASs following virologic failure.

**Study assessments.** Hepatitis C virus genotype and subtype were determined using the VERSANT HCV Genotype INNO-line probe assay 2.0 Assay (Siemens Healthcare GmbH, Erlangen, Germany). Patients who could not be subtyped using this assay were subtyped using the TrueGT test (Janssen Diagnostics, LLC, Raritan, NJ, USA). HCV genotype and subtype at baseline were further assessed by NS5B sequence-based Basic Local Alignment Search Tool analysis. A phylogenetic tree was generated from the NS5B sequences using neighbor joining method.

Hepatitis C virus RNA (determined by COBAS TaqMan HCV Test v2.0 for use with the High Pure System assay; Roche Molecular Diagnostics, Pleasanton, CA, USA) was measured at screening, baseline, and at weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 on-treatment (as applicable) and weeks 4, 12, and 24 post-treatment.

Plasma samples were collected at each visit for viral sequence analysis, as well as at any unscheduled visit to confirm on-treatment or post-treatment virologic failure. For viral resistance monitoring, HCV NS5B coding regions were amplified using standard reverse transcription polymerase chain reaction technology, and deep sequencing assays were performed using the Illumina MiSeq Platform (Illumina, San Diego, CA, USA) by the WuXi Genome Center (Shanghai, China). NS5B nucleotide inhibitor RASs were defined as substitutions that conferred > 2.5-fold reduced susceptibility *in vitro* or emerged in HCV replicon or patients with virologic failure in responding to NS5B nucleotide inhibitors (S96T, N142T, L159F, E237G, S282T, any S282 variant other than T, C/M289I/L, L320F/I/V, and V321A/I) and are reported at a 15% cutoff.

Blood samples for pharmacokinetic analysis were collected from patients at each on-treatment visit after baseline (as detailed previously for HCV-RNA). Drug concentrations were determined using fully validated high-performance liquid chromatography/tandem mass spectrometry bioanalytical methods.

![Figure 1: Patient disposition.](image-url)

*Reasons for not meeting inclusion criteria can be found in Table S1. AE, adverse event.*
Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory analyses, vital signs measurements, electrocardiograms, and physical examinations.

**Statistical analyses.** Patients were grouped according to treatment regimen. All statistical summaries and analyses were performed using SAS software (SAS Institute, Cary, North Carolina, USA). Sample sizes were based on the length of the 95% exact confidence intervals (CI) and assumed SVR12 rates of 90% for genotype 2 (sofosbuvir plus ribavirin 12 weeks), 85% for genotype 3 (sofosbuvir plus ribavirin 24 weeks), 80% for genotypes 1 and 6 (interferon-ineligible and interferon-intolerant; sofosbuvir plus ribavirin 24 weeks), and 90% for genotypes 1 and 6 (sofosbuvir plus peginterferon/ribavirin 12 weeks).

Efficacy and safety analyses included all enrolled patients who received at least one dose of study drug. A two-sided 95% exact CI was calculated for SVR12 rates using the Clopper–Pearson method. Subgroup analyses of SVR12 by baseline demographics and disease characteristics were performed. Patients were analyzed according to their reported cirrhosis status. Safety data were summarized descriptively. AEs were coded using the Medical Dictionary for Regulatory Activities, version 19.1.

The pharmacokinetic population included all patients who received at least one dose of study drug for whom sofosbuvir and GS-331007 concentration data were available. Population pharmacokinetic parameters (area under the plasma concentration vs time curve over the dosing interval \[AUC_{\text{tau}}</script> and maximum observed plasma concentration of drug \([C_{\text{max}}]\) were computed using previously established pharmacokinetic models. Results were compared with data from the historical control from sofosbuvir phases 2 and 3 studies (sofosbuvir US New Drug Application [NDA] population). Geometric least squares means ratios (GMRs) and 90% CIs were calculated.

**Results**

**Patients.** The study was conducted from June 25, 2015 to November 03, 2016 at 26 centers across China. Of the 479 patients screened, 389 were enrolled and received at least one dose of study drug. The majority of screen failures (87%) did not meet eligibility criteria (Fig. 1 and Table S1).

Overall, the mean age was 43 years, 50% were male, and all were Asian (Table 1). In total, 59 patients (15%) had cirrhosis at baseline, and the majority of patients had the IL28B CC allele (77%). Of the 163 patients with genotype 1 HCV, 161 had genotype 1b, and two had genotype 1a. Of the 64 patients with genotype 2, 63 had genotype 2a; one patient had genotype 1b by NS5B sequencing suggestive of possible genotype 2/genotype 1b.

**Table 1** Baseline demographic and disease characteristics

| Genotype 1 | Genotype 6 | Genotype 2 | Genotype 3 |
|------------|------------|------------|------------|
| Sofosbuvir plus peginterferon/ribavirin 12 weeks (n = 98) | Sofosbuvir plus peginterferon/ribavirin 12 weeks (n = 32) | Sofosbuvir plus peginterferon/ribavirin 12 weeks (n = 4) | Sofosbuvir plus peginterferon/ribavirin 12 weeks (n = 64) |
| Sofosbuvir plus peginterferon/ribavirin 24 weeks (n = 65) | Sofosbuvir plus peginterferon/ribavirin 24 weeks (n = 4) | Sofosbuvir plus peginterferon/ribavirin 24 weeks (n = 126) |

| Mean, years (range) | Male sex, n (%) | Mean BMI, kg/m² (range) | Cirrhosis, n (%) | IL28B genotype, n (%) | HCV-RNA Mean, log_{10} IU/mL (range) | HCV treatment-experienced, n (%) | Response to prior HCV treatment, n (%) |
|---------------------|-----------------|------------------------|-----------------|---------------------|-------------------------------|-----------------|-------------------------------|
| 41 (19–72) | 55 (56) | 23.6 (16.2–35.9) | 10 (10) | CC 62 (63) | 6.5 (4.3–7.6) | 42 (43) | Relapse/breakthrough 22/42 (52) |
| 51 (21–74) | 25 (38) | 23.5 (17.7–32.9) | 15 (47) | CT 35 (36) | 6.5 (4.5–7.9) | 51 (78) | Non-response 20/42 (48) |
| 38 (24–54) | 23.3 (17.3–32.0) | 2.6 (6) | 0 | TT 1 (1) | 6.5 (4.0–7.5) | 10 (31) | Interferon-intolerant 0 |
| 36 (32–40) | 19.8 (17.3–23.5) | 0 | 0 | 1 (2) | 6.5 (4.5–7.9) | 2 (50) | 0 |
| 48 (19–79) | 23.8 (18.1–32.5) | 8 (13) | 0 | 46 (65) | 6.5 (4.5–7.9) | 21 (37) | 0 |
| 40 (23–62) | 22.7 (16.7–34.0) | 24 (19) | 1 | 31 (97) | 6.2 (4.4–7.1) | 2 (50) | 10/20 (50) |

BMI, body mass index; HCV, hepatitis C virus.
recombinant virus. Of the 126 patients with genotype 3, 58 had genotype 3a, and 68 had genotype 3b. Among the 36 patients assigned as genotype 6, 33 had genotype 6a and 3 genotype 6c-l. A greater proportion of patients with HCV genotype 1 (57%) had received prior HCV treatment compared with the other genotypes (29–33%).

**Efficacy.** Sustained virologic response at 12 weeks after the end of treatment rates across the treatment groups ranged from 92% (genotype 2; sofosbuvir plus ribavirin for 12 weeks) to 100% (genotype 6; sofosbuvir plus ribavirin for 24 weeks) (Fig. 2a). A similar proportion of patients with genotype 1 achieved SVR12 when treated with sofosbuvir plus peginterferon/ribavirin for 12 weeks (94%) or sofosbuvir plus ribavirin for 24 weeks (95%); for those with genotype 1b, the results were 94% and 95%, respectively. SVR12 rates were 97% and 100% for patients with genotype 6 treated with sofosbuvir plus peginterferon/ribavirin for 12 weeks or sofosbuvir plus ribavirin for 24 weeks, respectively. High SVR12 rates were also observed for patients with genotype 2 (92%) and genotype 3 (95%) who received sofosbuvir plus ribavirin for 12 weeks or 24 weeks, respectively (Table 2). Two patients were not on-treatment viral breakthroughs. In total, 20/389 (5%) patients experienced relapse within 12 weeks of completing treatment. Of these, nine were treated with sofosbuvir plus ribavirin for 24 weeks, seven with sofosbuvir plus peginterferon/ribavirin for 12 weeks, and four with sofosbuvir plus ribavirin for 12 weeks (Table 2).

**Virologic analysis.** Baseline NS5B sequences were successfully obtained for 380 patients. Phylogenetic analysis showed that a diverse group of genotypes (1b, 1a, 2a, 3a, 3b, and 6a) were included in this study (Fig. 3). Of note, among genotype 3 patients, 54% had genotype 3b. At baseline, three of 380 patients had NS5B RASs; two with NS5B V321I or M289I achieved SVR following treatment with sofosbuvir plus peginterferon/ribavirin and sofosbuvir plus ribavirin, respectively. One patient with L159F at baseline relapsed and the L159F was also detected at the time of relapse. Of the remaining 19/20 patients with relapse following sofosbuvir-based treatment, none had NS5B RASs at baseline. Two patients did not have sequencing data available at virologic failure. For the 17 patients with sequencing results at virologic failure, no RASs were found.

**Pharmacokinetics.** The administration of 400 mg of sofosbuvir in a Chinese population provided comparable plasma exposures of sofosbuvir and GS-331007 to those observed in the sofosbuvir phases 2 and 3 populations of the US NDA.

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**Figure 2** Proportion of patients achieving sustained virologic response at 12 weeks post-treatment (SVR12). (a) Overall SVR12 by genotype (NC, no cirrhosis). Error bars represent 95% confidence intervals. C, cirrhosis; NC, no cirrhosis.

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Subgroup analyses found SVR rates ≥ 86% across treatment groups, irrespective of most baseline characteristics, such as IL28B genotype, baseline HCV-RNA level, and prior HCV treatment history (Table S2). Numerically lower SVR12 rates were, however, observed in patients receiving the peginterferon-containing regimen who had cirrhosis (Fig. 2b): 7/10 patients with genotype 1 (70%) and 1/2 patients with genotype 6 (50%) achieved SVR12. Additionally, a non-CC IL28B subtype was associated with reduced SVR12 in patients with HCV genotype 1 treated with sofosbuvir plus peginterferon/ribavirin versus sofosbuvir plus ribavirin only: 83% (30/36) versus 95% (19/20), respectively (Table S2).

One patient had a genotype correction after baseline NS5B sequencing; the patient was determined to have genotype 1b HCV infection after having been assigned genotype 2 at screening. After 12 weeks of sofosbuvir plus ribavirin, this patient achieved SVR12.
Three patients discontinued treatment because of AEs: fatal cerebral hemorrhage (sofosbuvir plus ribavirin 12 weeks), cerebral infarction (sofosbuvir plus peginterferon/ribavirin 12 weeks), and mental disorder (sofosbuvir plus ribavirin 24 weeks). Of these, the Grade 2 mental disorder was the only serious AE considered treatment-related and resolved after discontinuation of study drug.

Discussion

Annual reports on health statistics from the Chinese Ministry of Health show that newly reported cases of HCV infection have been increasing year-on-year, from 21 000 cases in 2003 to over 200 000 in 2012. Of these patients, many are treated with the standard of care peginterferon/ribavirin regimens but do not achieve SVR. Besides lack of efficacy, the reasons for treatment failure include discontinuation of treatment due to unmanaged or unmanageable side effects and problems with the monitoring of patients in rural areas. The current study provides the largest data sets examining the efficacy of sofosbuvir-containing HCV treatments in a Chinese population infected with HCV genotype 1, 2, 3, or 6. Overall, sofosbuvir-based therapy resulted in high SVR rates of ≥92%.

The response rates with sofosbuvir plus peginterferon/ribavirin in HCV genotype 1 and subtype 1b (both 94%) observed in this study were higher than the rates reported in the phase 3 NEUTRINO study (89% and 82%, respectively). Patients with the IL28B CC genotype respond better to interferon-based regimens than those with the CT or TT genotype, and up to 88% of Chinese patients reportedly carry the CC allele. In this study, 77% of patients had IL28B CC genotype versus 29% of patients in

Table 2  Virologic response following treatment

| Response† | Genotype 1 | Genotype 6 | Genotype 2 | Genotype 3 |
|-----------|------------|------------|------------|------------|
|           | Sofosbuvir plus peginterferon/ribavirin 12 weeks (n = 98) | Sofosbuvir plus ribavirin 24 weeks (n = 65) | Sofosbuvir plus peginterferon/ribavirin 12 weeks (n = 32) | Sofosbuvir plus ribavirin 24 weeks (n = 4) |
| HCV-RNA < LLOQ | Baseline | 0 | 0 | 0 | 0 |
|               | On-treatment week 2 | 92/98 (94) | 52/65 (80) | 32/32 (100) | 4/4 (100) |
|               | On-treatment week 4 | 98/98 (100) | 65/65 (100) | 32/32 (100) | 4/4 (100) |
|               | On-treatment week 12 | 97/97 (100) | 65/65 (100) | 32/32 (100) | 3/3 (100) |
|               | On-treatment week 24 | NA | 65/65 (100) | NA | 3/3 (100) |
|               | SVR4 | 93/98 (95) | 62/65 (95) | 32/32 (100) | 4/4 (100) |
|               | SVR12 | 92/98 (94) | 62/65 (95) | 31/32 (97) | 4/4 (100) |
|               | [95% CI] | [87–98] | [87–99] | [84–100] | [40–100] |
| Reasons for virologic failure | Relapse | 0/98 (0) | 3/65 (5) | 1/32 (3) | 0/4 |
|               | Death | 0/98 | 0/65 | 0/32 | 0/32 |
|               | SVR4 | 6/64 (9) | 6/64 (9) | 6/64 (9) | 6/64 (9) |
|               | [95% CI] | [83–97] | [90–96] | [120–126] | [120–126] |

†All values are n (%) unless stated otherwise.

CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantification; NA, not applicable; SVR, sustained virologic response; SVR4, SVR at 4 weeks post-treatment; SVR12, SVR at 12 weeks post-treatment.

Three patients discontinued treatment because of AEs: fatal cerebral hemorrhage (sofosbuvir plus ribavirin 12 weeks), cerebral infarction (sofosbuvir plus peginterferon/ribavirin 12 weeks), and mental disorder (sofosbuvir plus ribavirin 24 weeks). Of these, the Grade 2 mental disorder was the only serious AE considered treatment-related and resolved after discontinuation of study drug.

Figure 3  Phylogenetic tree of hepatitis C virus isolates from patients in the study generated using NS5B sequences. Each color line represents the baseline NS5B sequence from an individual patient.
In addition, the genotype 1 patients in this study had other baseline characteristics associated with positive treatment response: the majority (57%) was treatment naïve, younger (mean 41 years), and leaner (mean body mass index 24 kg/m²), and all but two had subtype 1b infection. The high rate of response suggests that 12 weeks of sofosbuvir plus peginterferon/ribavirin may be appropriate in certain patient populations. However, interferon-containing regimens are limited by low patient acceptability and require frequent laboratory monitoring.

Of note, a 95% SVR rate was observed in genotype 3 patients who received 24 weeks of all-oral sofosbuvir plus ribavirin. This was substantially higher than the rate of 84% seen in the VALENCE trial, which was conducted entirely in Europe. In our study, 81% of patients infected with genotype 3 had IL28B CC as compared with just 34% in VALENCE. Moreover, fewer of our patients were treatment-experienced (29% vs 58%, respectively). Such a high response rate is comparable with the SVR rate achieved with sofosbuvir plus daclatasvir for 12 weeks (90% in treatment naïve and 86% in treatment-experienced patients). Among the genotype 3 patients, genotype 3b was much more common (54%) here than in the USA and Europe (< 1%). However, the high prevalence of genotype 3b did not affect the SVR₁₂ rate achieved with 24 weeks of sofosbuvir plus ribavirin.

The high SVR₁₂ rates in patients with genotype 6 (97–100%) observed in this study are consistent with those reported in NEUTRINO and more recently in studies conducted in Hong Kong and Vietnam. Similarly, the SVR₁₂ rate of 92% in genotype 2 is consistent with the rates previously reported in phases 2 and 3 Western studies and similar to that seen in a study conducted in Japan.

As would be expected from the known safety profile of peginterferon/ribavirin, a greater proportion of patients in the sofosbuvir plus peginterferon/ribavirin group (94%) experienced AEs, Grade 3 or 4 AEs, and hematological abnormalities compared with those treated with sofosbuvir plus ribavirin only. Increasing treatment duration with sofosbuvir plus ribavirin from

### Table 3 AEs observed in each treatment arm

| Event, n (%) | Sofosbuvir plus peginterferon/ribavirin 12 weeks (n = 130) | Sofosbuvir plus ribavirin 12 weeks (n = 64) | Sofosbuvir plus ribavirin 24 weeks (n = 195) |
|-------------|----------------------------------------------------------|------------------------------------------|-------------------------------------------|
| Any AE      | 122 (94)                                                 | 54 (84)                                  | 152 (78)                                  |
| Treatment-related AE | 119 (92)                                                 | 36 (56)                                  | 115 (59)                                  |
| Serious AE  | 5 (4)                                                    | 1 (2)                                    | 4 (2)                                     |
| Discontinuation of treatment owing to an AE | 1 (1)                                                    | 1 (2)                                    | 1 (1)                                     |
| Death†     | 0                                                        | 1 (2)                                    | 0                                         |
| Common AEs‡ |                                                          |                                          |                                           |
| Pyrexia     | 48 (37)                                                  | 3 (5)                                    | 9 (5)                                     |
| Platelet count decreased | 37 (28)                                                  | 1 (2)                                    | 2 (1)                                     |
| Neutrophil count decreased | 37 (28)                                                  | 1 (2)                                    | 1 (1)                                     |
| White blood cell count | 33 (25)                                                  | 1 (2)                                    | 0                                         |
| Reticulocyte count increased | 13 (10)                                                  | 15 (23)                                  | 35 (18)                                   |
| Leukopenia  | 30 (23)                                                  | 2 (3)                                    | 6 (2)                                     |
| Anemia      | 26 (20)                                                  | 7 (11)                                   | 22 (11)                                   |
| Neutropenia | 23 (18)                                                  | 0                                        | 3 (2)                                     |
| Blood bilirubin increased | 7 (5)                                                    | 7 (11)                                   | 34 (17)                                   |
| Upper respiratory tract infection | 11 (8)                                                   | 10 (16)                                  | 26 (13)                                   |
| Asthenia    | 21 (16)                                                  | 2 (3)                                    | 9 (5)                                     |
| Headache    | 19 (15)                                                  | 4 (6)                                    | 12 (6)                                    |
| Myalgia     | 19 (15)                                                  | 1 (2)                                    | 1 (1)                                     |
| Hemoglobin decreased | 19 (15)                                                  | 8 (13)                                   | 19 (10)                                   |
| Fatigue     | 18 (14)                                                  | 3 (5)                                    | 15 (8)                                    |
| Insomnia    | 3 (2)                                                    | 3 (5)                                    | 24 (12)                                   |
| Dizziness   | 14 (11)                                                  | 2 (3)                                    | 11 (6)                                    |
| Thrombocytopenia | 17 (13)                                                  | 0                                        | 3 (2)                                     |
| Grade 3 or 4 hematology laboratory abnormalities |                                           |                                          |                                           |
| Decreased hemoglobin | 19 (15)                                                  | 1 (2)                                    | 18 (9)                                    |
| Decreased lymphocyte count | 6 (5)                                                    | 0                                        | 4 (2)                                     |
| Decreased neutrophil count | 15 (12)                                                  | 0                                        | 0                                         |
| Decreased platelet count | 1 (1)                                                    | 0                                        | 1 (1)                                     |
| Decreased white blood cell count | 7 (5)                                                    | 0                                        | 1 (1)                                     |

†Treatment-unrelated death from a cerebral hemorrhage.
‡The listed AEs occurred in at least 10% of the patients in any group.
AE, adverse event.
12 to 24 weeks did not affect AE incidence (84% and 78%, respectively). The pharmacokinetic findings from the current study demonstrate comparable sofosbuvir and GS-331007 exposures in a Chinese population compared with the participants in the phases 2 and 3 sofosbuvir studies included in the US NDA. 25

Baseline RASs were found in only one patient (1/380; < 1%), who did not achieve SVR (L159F), and no emergent RASs were found in any of the other 17 patients who relapsed and had available sequencing data. A recent study evaluated the prevalence of L159F in virologic failures from sofosbuvir studies. Of the 353 patients that failed treatment, 15% had the L159F mutation, but this RAS did not seem to affect the efficacy of a sofosbuvir-based retreatment regimen for these patients. 32 The S282T variant that is associated with sofosbuvir resistance in vitro 33 was not detected in any of the patients who experienced virologic failure and had post-treatment sequencing data.

The main limitation of the study was the lack of control arms. Also, genotypes 1 and 6 patients were assigned to peginterferon-based therapy unless they were interferon-ineligible, meaning patient numbers in the peginterferon-free treatment groups for these two genotypes were lower compared with peginterferon-containing groups. Overall, the number of genotype 6 patients enrolled in the study was low.

The results from this phase 3b study indicate that sofosbuvir-based regimens represent a highly effective treatment option for Chinese patients with HCV genotype 1, 2, 3, or 6 infection. Both sofosbuvir plus peginterferon/ribavirin for 12 weeks and all-oral sofosbuvir plus ribavirin for 12–24 weeks would represent, in China, a clinically significant improvement compared with the current standard of care of peginterferon/ribavirin.

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### Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

**Table S1.** Screen failure patients who did not meet eligibility criteria.

**Table S2.** Subgroup analyses of SVR12 by baseline disease characteristics.

**Table S3.** Comparisons of mean (%CV) SOF and GS-331007 exposures and creatinine clearance between HCV-infected patients in China and the SOF US NDA Phase 2/3 population (pharmacokinetic population).