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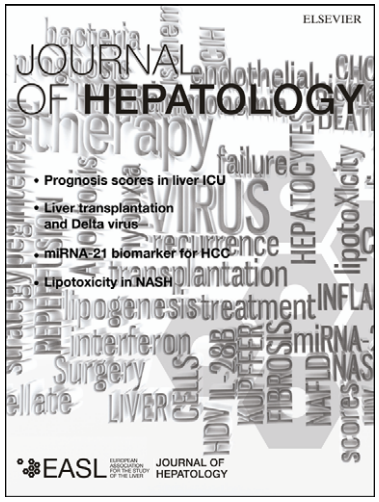

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Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naïve patients with HCV genotype 1: a randomized, 28-day, dose-ranging trial

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List of abbreviations in the order of appearance:

HCV: Hepatitis C virus

peg-IFN: Pegylated interferon

RBV: Ribavirin

RVR: Rapid virologic response

SVR: Sustained virologic response

IL: Interleukin

LOD: Limit of detection

MedDRA: Medical Dictionary for Regulatory Activities

ECG: Electrocardiogram

AUC_{0-tau}: Area under the concentration-time curve from time 0 to the end of dosing interval

C_{max}: Maximum plasma concentration

t_{max}: Time to C_{max}

$t_{½}$: Elimination half-life

HOMA-IR: Homeostasis model assessment of insulin resistance

CI: Confidence interval

Conflict of interest and Financial support

Dr Rodriguez-Torres reports receiving consultancy fees from Akros Pharmaceutical, Bristol-Myers Squibb, Genentech, Hoffman-La Roche, Inhibitex, Janssen R & D Ireland, Merck Sharp & Dohme Corp., Pharmasset, Santaris Pharma. A/S, Vertex Pharmaceutical Inc, and research/grant support from Abbott Laboratories, Akros Pharmaceutical, Anadys Pharmaceutical, Beckman Coulter, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, Gilead Pharmaceuticals, GlaxoSmithKline, Hoffman-La Roche, Human Genome Sciences, Idenix Pharmaceutical, Idera Pharmaceutical, Inhibitex, Johnson & Johnson, Merck Sharp & Dohme Corp., Mochida Pharmaceutical, Novartis, Pfizer, Pharmasset, Santaris Pharma. A/S,

Scynexis, Inc., Siemens Healthcare Diagnostics, Vertex Pharmaceutical Inc. and Zymogenetics.

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Trial registration number: NCT01054729

ABSTRACT

Background and aims. Sofosbuvir (formerly GS-7977) is a pyrimidine nucleotide analog inhibitor of the hepatitis C virus (HCV) NS5B polymerase. We assessed the safety, tolerability, antiviral activity, and pharmacokinetics of sofosbuvir plus pegylated-interferon (peg-IFN)/ribavirin (RBV) in a 28-day, dose-ranging trial in treatment-naïve patients infected with genotype 1 HCV.

Methods. In this double-blind study, 64 patients were randomized (1:1:1:1) to receive one of three once-daily doses of oral sofosbuvir (100, 200, or 400 mg) or placebo plus peg-IFN/RBV for 28 days, after which all patients continued to receive peg-IFN/RBV alone for a further 44 weeks.

Results. Patients in the sofosbuvir/peg-IFN/RBV groups experienced mean reductions in HCV RNA >5 $\log_{10}$ IU/mL (-5.3 for 100 mg, -5.1 for 200 mg and -5.3 for 400 mg) vs -2.8 $\log_{10}$ IU/mL for placebo/peg-IFN/RBV after 28 days. Rapid virologic response (RVR) rates were markedly higher after sofosbuvir treatment (88–94%) than placebo (21%), as were rates of sustained virologic response (SVR) at post-treatment Week 24 (56%, 83%, and 80% for sofosbuvir 100, 200, and 400 mg, respectively, vs 43% for placebo). The number of patients experiencing virologic breakthrough and post-treatment relapse were higher in the sofosbuvir 100 mg group than sofosbuvir 200 and 400 mg groups. Sofosbuvir was well tolerated; the most frequent adverse events were fatigue and nausea.

Conclusions. These results support further studies with sofosbuvir at 200 mg and 400 mg to determine the optimal dose and treatment duration of sofosbuvir in HCV genotype 1. (Clinicaltrials.gov: NCT01054729)

Key words: Sofosbuvir, Hepatitis C virus, antiviral, rapid virologic response, sustained virologic response

INTRODUCTION

The recent approval of the hepatitis C virus (HCV) protease inhibitors telaprevir and boceprevir has inaugurated a new era in the treatment of HCV infection. These agents have raised the rates of sustained virologic response (SVR) for patients with genotype 1 HCV by as much as 30% in comparison with the former standard-of-care, pegylated-interferon (peg-IFN) combined with ribavirin (RBV) [1, 2]. However, the current protease inhibitor-based regimens are limited by lower rates of response in non-responders to prior therapy, the emergence of resistant mutations, and significant adverse events [2-4]. Thus, there remains a significant unmet need for potent antiviral agents with pangenotypic sensitivity, a high barrier to resistance, and fewer side effects for patients with HCV.

There are currently a large number of agents in development across a variety of classes for the treatment of HCV. One class for which promising in vitro results have been reported are the nucleoside/nucleotide analogs [1, 5]. These compounds share properties with the intracellular nucleoside substrates of the target HCV enzymes involved in the transcription of the viral genome and, when phosphorylated to the nucleoside-triphosphate, lead to premature termination of the growing HCV RNA chain during viral replication [6, 7]. Sofosbuvir (formerly GS-7977) is a phosphoramidate prodrug of beta-D-2'-deoxy-2'-fluoro-2'-C-methyluridine 5'-monophosphate with enhanced antiviral potency compared with earlier nucleoside analogs [8]. Sofosbuvir was initially studied as one of the two isomers of GS-9851 [9].

In the present study, we assess the safety, tolerability, antiviral activity, and pharmacokinetics of three different doses of sofosbuvir in combination with peg-IFN/RBV in treatment-naïve patients infected with genotype 1 HCV.

MATERIALS AND METHODS

Study Population

We enrolled 64 treatment-naïve patients with chronic HCV genotype 1 infection (HCV RNA levels ≥100,000 IU/mL at screening), 18–65 years of age with a body mass index of 18–36 kg/m^2. Females of childbearing potential were required to use a protocol-approved method of contraception. A liver biopsy within 3 years of dosing was required to exclude cirrhosis. Patients were otherwise in good health, with no significant co-morbidities. Other key exclusion criteria included positive test for hepatitis B surface antigen, anti-hepatitis B core protein IgM antibodies and anti-human immunodeficiency virus antibodies.

Informed consent was obtained from each patient included in the study. Local Ethics Review Committees provided approval for the study, which was conducted in accordance with Good Clinical Practice and the ethical guidelines of the 1975 Declaration of Helsinki.

Study Design

This randomized, placebo-controlled, double-blind dose-ranging study (Clinicaltrials.gov: NCT01054729) was conducted from 18 January 2010 to 25 August 2011 at seven sites in the United States (and Puerto Rico). Oral sofosbuvir or matching placebo (both manufactured by Metrics Inc, NC, USA on behalf of Gilead Sciences, Inc) were administered with peg-IFN alfa-2a (Pegasys®, Genentech, San Francisco, CA, USA) and RBV (Copegus®, Genentech,

San Francisco, CA, USA). Both peg-IFN and RBV were administered according to the package insert for patients with genotype 1 infection.

Eligible patients were randomized in a ratio of active : placebo of 1:1:1:1 to receive one of three once-daily doses of sofosbuvir (100, 200, or 400 mg) or placebo plus peg-IFN/RBV for 28 days, after which patients continued treatment with peg-IFN/RBV alone for a further 44 weeks. Both investigators and patients were blinded to the treatment assignment. Randomization was stratified by interleukin (IL) 28B status (rs12979860) for CC or CT/TT allele. The randomization schedule was provided by PharStat, Inc (NC, USA). Patients were randomized by a central web-based system using permutated blocks. Patients attended regular visits until the end of the 48 weeks period and follow-up took place 12 and 24 weeks after the last dose of peg-IFN/RBV to assess for SVR.

Patients were to have all therapy discontinued if there is inadequate response to therapy with PEG-IFN and RBV according to the following stopping rules: if HCV RNA is still detectable at Week 12, therapy should be continued until Week 24; if HCV RNA is still detectable at Week 24, therapy with PEG-IFN and RBV should be discontinued. The subject should then have an early termination visit approximately 30 days after all therapy is discontinued.

Assessment of Efficacy

Efficacy endpoints included change in circulating HCV RNA over 28 days of dosing, rates of rapid virologic response (HCV RNA below the limit of detection at Week 4), and rates of sustained virologic response at 12 (SVR12) and 24 (SVR24) weeks following completion of 48 weeks of treatment.

Blood samples to quantify plasma HCV RNA were collected at screening and in the morning (pre-dose on dosing days) on Days 1, 2, 4, 8, 15, 22, 28 and 29 and Weeks 6, 8, 12, 24, 48, 52, 60 and 72 (SVR24 visit). Blood samples for NS5B genotypic and phenotypic monitoring were collected (pre-dose on dosing days) at Days 0, 7, 14, 21 and 28 and Weeks 12, 20, 24, 28, 32, 36, 40, 44, 48, 52, 60 and 72 (SVR24 visit).

Hepatitis C virus genotyping and genotypic monitoring were performed as previously described [9]. Resistance monitoring was completed in all patients who received sofosbuvir and were classified as non-responders or rebounders, had virologic breakthroughs, or those with a plateau in HCV viral load between Day 1 and Day 28. Sequencing and phenotypic analyses were performed at 4-week intervals (for up to 48 weeks) in patients who had mutations leading to sofosbuvir resistance in order to determine the time for the resistant virus to return to background levels. Phenotypic assays to monitor resistance to sofosbuvir were performed on baseline (pre-dose on Day 1) and end-of-treatment samples.

All patients were assessed for rapid virologic response (RVR) (defined as HCV RNA <limit of detection, LOD [15 IU/mL] at Day 28) and viral breakthrough (defined as HCV RNA increase >LOD in two or more consecutive visits after an initial drop to below detection). Efficacy assessments included sustained virologic response, defined as HCV RNA below the LOD at 12 (SVR12) and 24 weeks (SVR24) following the last dose of study medication, and viral relapse, defined as HCV RNA >LOD after an initial drop to below detection by the end of treatment visits.

Safety Analysis

The primary endpoints were safety and tolerability of 28 days of treatment with sofosbuvir/peg-IFN/RBV. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary [10]. Vital signs were measured at screening and Days 1, 2, 4, 8, 15, 22, and 28. Twelve-lead electrocardiograms (ECGs) were recorded at screening and pre and post-dose on Days 1 and 28. Clinical laboratory samples (for serum chemistry, hematology and urinalysis) were obtained at screening and Days 1, 4, 8, 15, 22 and 28.

Pharmacokinetic Sample Collection and Analysis

Blood samples for pharmacokinetic analysis were collected on Day 1 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours post-dose; pre-dose on Days 2, 4, 8, 15 and 22 and pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose on Day 28.

Plasma concentrations of sofosbuvir and GS-331007 (beta-D-2'-deoxy-2'-fluoro-2'-C-methyluridine 5'-monophosphate) were determined using a validated high-performance liquid chromatography-tandem mass spectroscopy method (QPS, LLC Newark, DE, USA). The linear range of the plasma assay was 5–5,000 ng/mL for sofosbuvir and 10–5,000 ng/mL for GS-331007. Pharmacokinetic parameters were derived from the time-concentration data by standard non-compartmental analysis using WinNonLin Version 5.2 (Pharsight Corporation, Mountain View, CA, USA). Derived plasma pharmacokinetic parameters for sofosbuvir and GS-331007 included: area under the concentration-time curve from time 0 to the end of dosing interval (AUC_{0-tau}), maximum plasma concentration (C_{max}), time to C_{max} (t_{max}) and elimination half-life ($t_{½}$).

Statistical Analysis

No formal analysis was performed to determine sample size or to assess safety data. HCV RNA values (IU/mL) were transformed to the logarithmic (base 10) scale (log_{10} IU/mL) and summary statistics were performed on log_{10} transformed data for each treatment by visit. The efficacy endpoints, RVR rates and proportion of patients with HCV RNA levels lower than LOD at end-of-treatment, SVR4, SVR12 and SVR24 rates, were analyzed for the following subgroups: HCV genotype (1a, 1b), IL28B genotype (CC, CT/TT), gender (male, female), race (black, non-black), ethnicity (Hispanic or latino, not Hispanic or latino), homeostasis model assessment of insulin resistance (HOMA-IR) score (≤3, >3), baseline HCV RNA level (≤800,000 IU/mL, >800,000 IU/mL).

Pharmacokinetic parameters were log_{10}-transformed before analysis. Accumulation was determined by comparing AUC_{0-tau} on Day 28 to Day 1. Accumulation was analyzed by mixed effects model with day as a fixed effect and patient as a random effect. A 90% confidence interval (CI) for the true difference on the log-scale across all patients was estimated.

RESULTS

Study Population Disposition and Demographics

The demographic characteristics of the study population were similar across treatment groups (Table 1); patients in the placebo/peg-IFN/RBV treatment group had higher mean weight and body mass index than those in the sofosbuvir/peg-IFN/RBV treatment groups. There were no notable differences between the treatment groups for any disease characteristic (Table 1). Of the 64 randomized patients, 63 received at least one dose of study medication and were included in the safety analysis: sofosbuvir 100 mg (16 subjects), sofosbuvir 200 mg (18

subjects), sofosbuvir 400 mg (15 subjects), and placebo (14 subjects). Sixty-two completed the sofosbuvir/peg-IFN/RBV treatment period. One patient in the sofosbuvir 200 mg arm withdrew consent before receiving the first dose of study medication, and another patient in the same arm was lost to follow-up. Forty-six patients completed the 44-week peg-IFN/RBV treatment period (Table 2).

Efficacy Results

On-treatment results

Patients receiving sofosbuvir co-administered with peg-IFN/RBV had substantially greater suppression of plasma HCV RNA than those receiving placebo/peg-IFN/RBV (**Fig. 1**). Mean change from baseline in HCV RNA at Day 28 was -5.3 $\log_{10}$ IU/mL for patients receiving sofosbuvir 100 mg, -5.1 $\log_{10}$ IU/mL for 200 mg, and -5.3 $\log_{10}$ IU/mL for 400 mg versus -2.8 $\log_{10}$ IU/mL for placebo/peg-IFN/RBV. Viral suppression was rapid; by Day 7 of treatment, patients receiving sofosbuvir experienced mean reductions of 3.49 $\log_{10}$ IU/mL in the 100-mg group, 4.03 $\log_{10}$ IU/mL in the 200-mg group, and 4.44 $\log_{10}$ IU/mL in the 400-mg group, vs 0.97 $\log_{10}$ IU/mL in the group receiving placebo plus peg-IFN and ribavirin. Near maximal suppression of HCV RNA levels was observed on Day 22 for the sofosbuvir/peg-IFN/RBV 200 mg and 400 mg treatment groups and by Day 28 in the sofosbuvir 100 mg/peg-IFN/RBV treatment group.

Rapid virologic response rates were markedly higher in patients receiving sofosbuvir at all dose levels compared with placebo (Table 3). Three of the four patients who received sofosbuvir and did not achieve RVR had unfavourable prognostic factors (non-CC IL28B alleles and baseline HCV RNA >800,000 IU/mL). One patient in the sofosbuvir 200 mg

group was lost to follow-up during the initial 28-day dosing period; this patient was classed as a treatment failure at all subsequent timepoints.

No viral breakthrough was observed in any patient receiving sofosbuvir during the 28-day dosing period. Eight patients experienced viral breakthrough during peg-IFN/RBV treatment (4 in the sofosbuvir 100 mg arm, 2 in the sofosbuvir 400 mg arm, and 2 in the placebo arm). All had baseline HCV RNA >800,000 IU/mL and most (7/8) had non-CC IL28B alleles.

Sustained virologic response

Patients in the sofosbuvir dose groups had higher rates of SVR than those treated with placebo/peg-IFN/RBV. SVR rates at post-treatment Week 24 were 56%, 83%, and 80% for sofosbuvir 100 mg, 200 mg, and 400 mg, respectively, versus 43% for peg-IFN/RBV (Table 3). One patient who completed treatment with sofosbuvir 400 mg/peg-IFN/RBV but discontinued peg-IFN/RBV on Day 29, achieved SVR12 and SVR24. This patient had genotype 1a HCV infection, the CC IL28B allele, and a baseline HCV RNA level of 1,740,000 IU/mL. Ten patients experienced viral relapse after the end of treatment, five who received sofosbuvir 100 mg, one each who received sofosbuvir 200 mg and 400 mg, and three who received placebo. All patients who received sofosbuvir and relapsed had baseline HCV RNA >800,000 IU/mL (range: 2,160,000-26,100,000 IU/mL) and most (6/7) had non-CC IL28B alleles.

Subgroup efficacy analysis showed that there was no effect of gender, race, ethnicity, HCV genotype, IL28B genotype, baseline HCV RNA levels or HOMA-IR score in the reduction of HCV RNA levels following 28 days of dosing with sofosbuvir/peg-IFN/RBV.

Resistance monitoring

The NS5B region of all 63 treated subjects was analyzed at baseline; the S282T mutation was not detected in any sample. Samples for the 12 patients who qualified for monitoring by the criteria specified in the methods section (non-responders or rebounders, those had virologic breakthrough, or HCV viral load plateaus between Day 1 and Day 28) were also analyzed. The S282T mutation was not detected in any of the samples at any of the timepoints tested. In addition, sequencing of the entire NS5B sequence from the virologic failures did not identify any mutation at positions 316, 414, 423, 482, 486, 495, 554, or 559, which have been previously reported to be associated with resistance to non-nucleoside inhibitors.

Safety Results

Fifty-four of the 63 study patients reported adverse events during the 28-day treatment period with sofosbuvir/peg-IFN/RBV, irrespective of dose. The most frequently reported adverse events during this period were fatigue, nausea, chills, headache, and arthralgia (Table 4). The frequency and intensity of adverse events was comparable between the sofosbuvir/peg-IFN/RBV treatment groups and the placebo/peg-IFN/RBV group. All adverse events were considered mild or moderate in intensity by the investigator; most (260/282; 92%) resolved. During the sofosbuvir plus peg-IFN/RBV treatment phase of the study, no serious adverse events and no adverse events that led to discontinuation of study medication were reported. However, during the peg-IFN/RBV treatment phase, five patients discontinued peg-IFN/RBV and five patients experienced a serious adverse event (one patient whose last dose was sofosbuvir 100 mg [peripheral ischemia]; three patients whose last dose was sofosbuvir 400 mg [acute pancreatitis; anemia; depression]; one patient whose last dose was placebo

[abdominal pain]). All serious adverse events occurred at least 50 days after the end of sofosbuvir treatment and all resolved.

Changes in hematologic parameters, including hemoglobin (**Fig. 2A**), erythrocytes, lymphocytes, basophils, eosinophils, neutrophils, (**Fig. 2B**) and platelets were similar in sofosbuvir and placebo arms and were consistent with changes observed during treatment with peg-IFN and ribavirin alone. No significant changes were observed in vital signs and ECG evaluations.

Pharmacokinetic Results

Following single or multiple dosing, sofosbuvir was absorbed rapidly with a median [range] t_{max} of 1 hour [0.5–3.0]. Sofosbuvir elimination was rapid with median $t_{½}$ in the range of 0.48–0.75 hours. GS-331007 exhibited a longer t_{max} (median [range]: 4 hours [1.5–8]) and half-life (median $t_{½}$ range: 7.27–11.80) than sofosbuvir. No significant accumulation of sofosbuvir or GS-331007 was observed (accumulation ratio close to 1).

DISCUSSION

In this dose-ranging study, treatment-naïve genotype 1 patients receiving sofosbuvir 100-400 mg and peg-IFN/RBV for 28 days followed by 44 weeks of peg-IFN/RBV experienced more rapid viral suppression and substantially higher rates of on-treatment and post-treatment response than patients receiving 48 weeks of peg-IFN/RBV. By Day 21 of treatment, all three sofosbuvir groups experienced mean reductions of >5 $\log_{10}$ IU/mL in HCV RNA compared to 2.2 IU/mL in patients receiving peg-IFN/RBV. Rates of rapid virologic response for patients in the sofosbuvir arms ranged from 88% to 94% vs 21% in patients receiving peg-IFN/RBV alone.

Although response during the 28-day, sofosbuvir/placebo phase of the study was nearly identical for all three sofosbuvir groups, differences begin to emerge during the peg-IFN/RBV phase of dosing. Four patients in the 100-mg group experienced viral breakthrough soon after the end of sofosbuvir dosing. By contrast, no patients in the 200-mg group and two in the 400-mg group experienced breakthrough during peg-IFN/RBV dosing. In post-treatment follow-up, the inadequacy of the 100-mg dose of sofosbuvir became more evident. Five patients in the 100-mg group relapsed almost immediately after the end of treatment, whereas only one patient each in the 200- and 400-mg groups relapsed during follow-up. The rate of SVR24 for the 100-mg group was 56% as compared to 83% and 80% for the 200- and 400-mg groups, respectively. As a result, the 200- and 400-mg doses were selected for further evaluation in Phase IIb trials.

The adverse events seen during this trial were those commonly observed during treatment with peg-IFN and RBV [11, 12]. During the 28-day dosing period, sofosbuvir was generally safe and well-tolerated with all adverse events classified as mild or moderate in intensity. Changes in hematology parameters relating to anemia (reductions in the levels of hemoglobin and erythrocytes) and neutropenia were consistent with those observed for peg-IFN/RBV [11, 12].

The marked antiviral activity and SVR rates observed with 28 days of sofosbuvir in combination with PEG+RBV suggest that sofosbuvir may be a beneficial component of a treatment regimen for patients with HCV. Further studies are warranted to determine the optimal sofosbuvir treatment duration, efficacy of sofosbuvir in other genotypes of HCV infection (2 to 6), and whether sofosbuvir can play a role in interferon-sparing treatment

regimens.

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FIGURE LEGENDS

Figure 1: **Sofosbuvir antiviral activity.** Mean HCV RNA decline over time. Error bars represent standard deviation.

Figure 2: **Results from the hematology laboratory tests.** (A) Mean hemoglobin change from baseline, and (B) absolute neutrophils mean change from baseline following sofosbuvir/peg-IFN/RBV or placebo/peg-IFN/RBV.

Figure 1

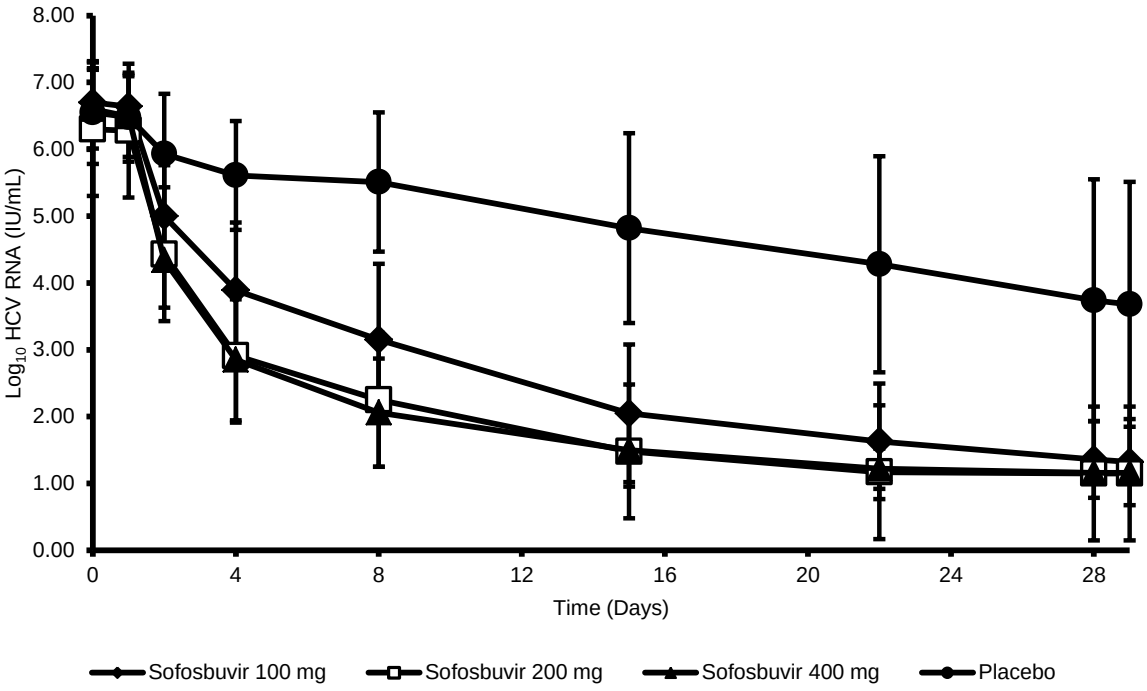
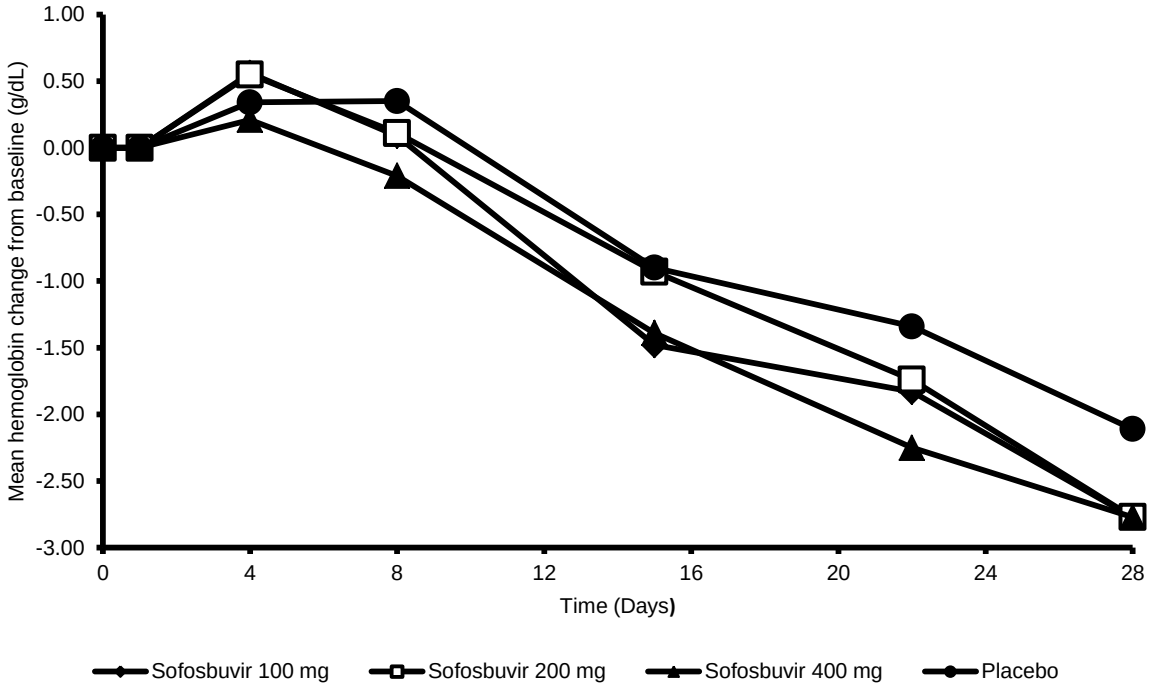


Figure 2

(A)



(B)

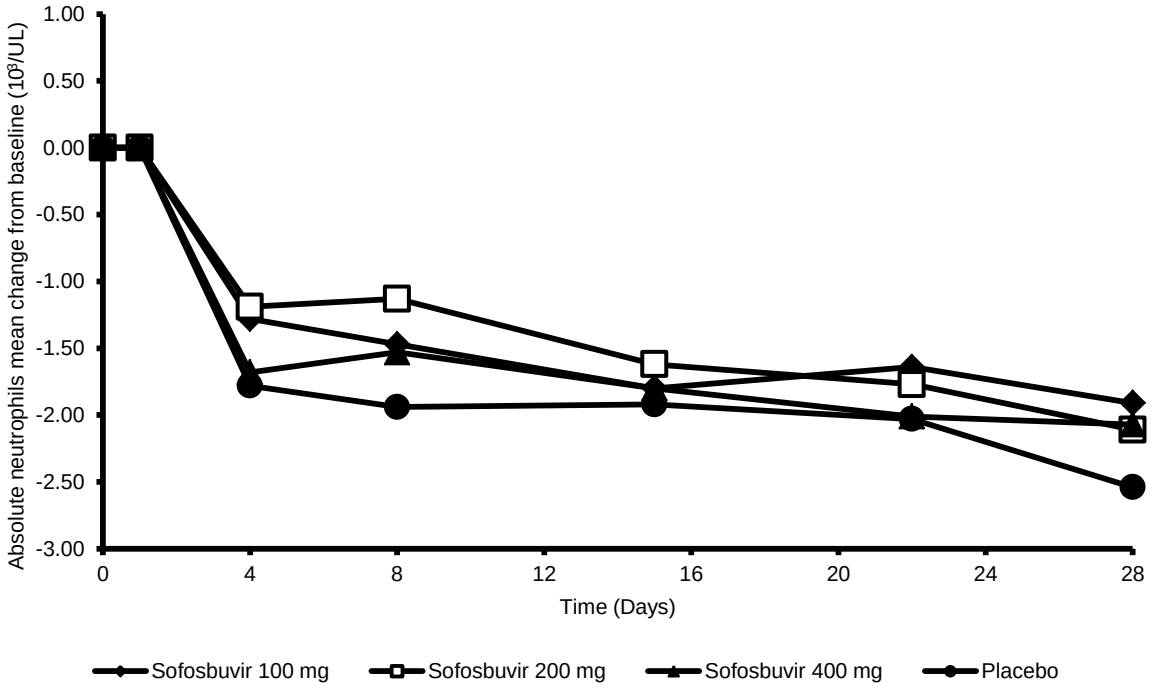


Table 1. Summary of demographic characteristics

Demographics	Sofosbuvir 100 mg (n = 16)	Sofosbuvir 200 mg (n = 18)	Sofosbuvir 400 mg (n = 15)	Placebo (n = 14)
Age (years); mean [range]	44.4 [23–57]	44.4 [30–57]	44.9 [29–62]	46.6 [27–62]
Sex; n (%)				
Male	11 (69)	10 (56)	11 (73)	11 (79)
Body mass index (kg/m^2); mean [range]	28.2 [20.5–35.1]	26.8 [19.3–35.5]	27.4 [19.7–35.6]	30.7 [23.3–35.6]
Weight (kg); mean [range]	80.4 [57.3–105.0]	76.4 [56.7–102.5]	76.3 [51.1–104.0]	91.2 [59.7–109.0]
Race; n (%)				
White/Caucasian	15 (94%)	16 (89%)	12 (80%)	14 (100%)
HCV 1a/1b; n/n	14/2	15/2	12/3	10/4
HCV RNA (log_{10} IU/mL); mean	6.64	6.28	6.49	6.48
IL28B CC; n (%)	4 (25%)	5 (28%)	4 (27%)	4 (29%)
HOMA-IR ≤3; n (%) [range]	10 (63%)	13 (72%)	7 (47%)	7 (50%)
No/minimal fibrosis (F0–1)	9 (56)	10 (56)	9 (60)	10 (71)
Portal fibrosis (F1–2)	6 (38)	4 (22)	4 (27)	2 (14)
Bridging fibrosis (F3)	1 (12)	4 (22)	2 (13)	2 (14)

HCV = hepatitis C virus; IL = interleukin; HOMA-IR = homeostasis model assessment of insulin resistance

Table 2. Patient Disposition

	Sofosbuvir 100 mg (n = 16)	Sofosbuvir 200 mg (n = 18)	Sofosbuvir 400 mg (n = 15)	Placebo (n = 14)
Number of subjects randomized	16	19	15	14
Number of subjects in safety population	16	18	15	14
Completed sofosbuvir treatment period, n (%)	16 (100%)	17 (94%)	15 (100%)	14 (100%)
Reasons not completed sofosbuvir treatment period, n (%)				
Lost to follow-up	0	1 (5.6%)	0	0
Completed 48 weeks of PEG+RBV, n (%)	12 (75%)	14 (78%)	9 (60%)	11 (79%)
Primary Reasons for Study Withdrawal, n (%)				
Adverse Event	1 (6%)	1 (6%)	2 (13%)	1 (7%)
Consent Withdrawn	1 (6%)	0	1 (7%)	0
Lost to Follow-up	0	1 (6%)	0	0
PEG/RBV non-response	2 (13%)		2 (13%)	2 (14%)
Other	0	2 (11.1%)	1 (7%)	0

Peg = pegylated; RBV = ribavirin

Table 3. Proportion of patients with hepatitis C virus RNA below the limit of detection at 28 days (rapid virologic response), end of treatment, and post-treatment

	Sofosbuvir 100 mg* (n = 16)	Sofosbuvir 200 mg* (n = 18)	Sofosbuvir 400 mg* (n = 15)	Placebo* (n = 14)
Day 28, n (%)	14 (88%)	17 (94%)	14 (93%)	3 (21%)
End of treatment[†], n (%)	14 (88%)	17 (94%)	13 (87%)	10 (71%)
SVR12, n (%, 95% CI)	9 (56%, 30-80%)	13 (72%, 47-90%)	13 (87%, 60-98%)	7 (50%, 23-77%)
SVR24, n (%, 95% CI)	9 (56%, 30-80%)	15[‡] (83%, 59-96%)	12 (80%, 52-96%)	6 (43%, 18-71%)

*Patients received sofosbuvir or placebo from Day 1 to Day 28 and peg-IFN/RBV from Day 1 to Week 48.
[†]End of treatment was defined as the last assessment collected while the patient was receiving study medication.
[‡]Two patients who achieved SVR24 are missing data for the post-treatment Week 12 time point.
The confidence intervals are calculated using Clopper-Pearson exact method.
CI = confidence interval; SVR = sustained virologic response

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Table 4. Adverse events reported by at least 10% of patients in any treatment group during the sofosbuvir treatment period

	Sofosbuvir 100 mg (n = 16)	Sofosbuvir 200 mg (n = 18)	Sofosbuvir 400 mg (n = 15)	Placebo (n = 14)
Any Event	14 (88%)	15 (83%)	13 (87%)	12 (86%)
Fatigue	7 (44%)	7 (39%)	8 (53%)	6 (43%)
Nausea	4 (25%)	5 (28%)	8 (53%)	5 (36%)
Chills	7 (44%)	6 (33%)	4 (27%)	2 (14%)
Headache	4 (25%)	6 (33%)	5 (33%)	2 (14%)
Arthralgia	7 (44%)	2 (11%)	3 (20%)	0
Pruritus	3 (19%)	1 (6%)	5 (33%)	1 (7%)
Insomnia	3 (19%)	2 (11%)	2 (13%)	2 (14%)
Anemia	0	6 (33%)	1 (7%)	1 (7%)
Decreased appetite	3 (19%)	1 (6%)	3 (20%)	1 (7%)
Dizziness	2 (13%)	1 (6%)	3 (20%)	2 (14%)
Myalgia	4 (25%)	1 (6%)	2 (13%)	1 (7%)
Pain	1 (6%)	2 (11%)	1 (7%)	3 (21%)
Abdominal pain	1 (6%)	0	2 (13 %)	2 (14%)
Affect lability	1 (6%)	1 (6%)	1 (7%)	2 (14%)
Anxiety	1 (6%)	1 (6%)	3 (20%)	0
Injection site reaction	1 (6%)	1 (6%)	1 (7%)	2 (14%)
Pyrexia	2 (13%)	1 (6%)	1 (7%)	1 (7%)
Depression	1 (6%)	1 (6%)	2 (13%)	0
Dermatitis	2 (13%)	1 (6%)	1 (7%)	0
Injection site erythema	1 (6%)	2 (11%)	0	1 (7%)
Oropharyngeal pain	0	3 (17%)	1 (7%)	0
Vomiting	0	0	3 (20%)	0