PDF created July 20, 2017, 7:46 am

var drug_url = "sofosbuvir-drug";

Sofosbuvir *(Sovaldi)*

See also
Ledipasvir-Sofosbuvir
,
Sofosbuvir-Velpatasvir
.

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Drug Summary

Sofosbuvir has been a breakthrough new medication for the treatment of patients with chronic hepatitis C. Sofosbuvir has a number of ideal properties, including pangenotypic activity, once daily dosing, no meal restrictions, few adverse effects, minimal drug-drug interactions, high genetic barrier to resistance, good safety and efficacy in patients with advanced liver disease, and excellent sustained virologic response rates in patients with unfavorable baseline characteristics. In the new AASLD-IDSA hepatitis C guidelines, the combination of sofosbuvir plus peginterferon plus ribavirin is the recommended regimen for patients with genotype 1,4,5, and 6 infection. In addition, for patients ineligible to receive interferon, sofosbuvir plus simeprevir (with or without ribavirin) is recommended, but this combination is not an FDA-approved regimen. For patients with genotype 2 or 3, the combination of sofosbuvir plus ribavirin is recommended. The use of sofosbuvir in combination with ribavirin provides the first FDA approved all oral therapy for hepatitis C. Of note, the activity against genotype 3 appears less than with genotype 2 and treatment of genotype 3

infection requires a longer all-oral course of treatment than with genotype 2. Sofosbuvir currently has a major role in the treatment of chronic HCV infection, but the extraordinarily high cost has served as a major barrier for more widespread use and treatment of persons with chronic HCV infection.

Class and Mechanism

Sofosbuvir (*Sovaldi*) is a nucleotide analog inhibitor of hepatitis C virus NS5B polymerase—the key enzyme mediating HCV RNA replication. Sofosbuvir is a prodrug and after ingestion it is rapidly converted to GS-331007, the predominant circulating drug that accounts for greater than 90% of the systemically active drug. The compound GS-331007 is efficiently taken up by hepatocytes, whereby cellular kinases convert GS-331007 to its pharmacologically active uridine analog 5'-triphosphate form (GS-461203). This triphosphate compound mimics the natural cellular uridine nucleotide and is incorporated by the HCV RNA polymerase into the elongating RNA primer strand, resulting in chain termination. The active form GS-461203 targets the NS5B catalytic site and acts as a non-obligate chain terminator. The active compound (GS-461203) does not inhibit host DNA polymerases, RNA polymerases, or mitochondrial RNA polymerase.

Manufacturer for United States

Gilead Sciences is the manufacturer for sofosbuvir (*Sovaldi*) (Figure 1). The drug sofosbuvir was previously known as GS-7977 and was originally developed by Pharmasset as compound PSI-7977. The medication PSI-7977 was discovered as the more active diastereoisomer of the parent compound PSI-7851.

Cost and Medication Access

The wholesale acquisition cost (WAC) for sofosbuvir is $1,000 per 400 mg pill. Accordingly, the cost for the sofosbuvir component in a 12-week treatment course is $84,000 (and the total regimen cost is depends on the other medications used in combination with sofosbuvir). For a 24-week course of sofosbuvir, the WAC is $168,000. Gilead Sciences has an active sofosbuvir patient assistance program for eligible patients with hepatitis C who do not have insurance and are not covered by Medicaid or Medicare. Information regarding the Gilead Sciences sofosbuvir patient assistance program can be obtained at the Support Path for *Solvaldi* and *Harvoni* web site and by contacting them directly by phone at 1-855-769-7284 (hours of operation Monday through Friday between 9:00 am and 8:00 pm Eastern Standard Time).

Adverse Effects

Sofosbuvir is generally well-tolerated. The most common adverse effects observed with sofosbuvir, when used in combination with ribavirin, have been fatigue and headache. Sofosbuvir is pregnancy category B. To report suspected adverse reactions, contact (1) Gilead Sciences, Inc. at

1-800-GILEAD-5 or (2) the FDA at 1-800-FDA-1088.

Key Drug Interactions

For complete information on sofosbuvir-related drug interactions, see the Drug Interactions section in the Sofosbuvir (*Sovaldi*) Prescribing Information.

Clinical Trials

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A1444-040 (Sofosbuvir plus Daclatasvir)

This complex study included 4 groups and total of 10 arms, with all treatment arms including a regimens of sofosbuvir plus the investigational NS5A replication complex inhibitor daclatasvir, with our without ribavirin. Both sofosbuvir and daclatasvir were administered as once daily oral dosing. The trial included treatment-naive and treatment-experienced patients with genotypes 1-3 chronic HCV. The four groups in the trial included (1) treatment-naive genotype 2 or 3 treated for 24 weeks, (2) treatment-naive genotype 1a or 1b treated for 24 weeks, (2) treatment-naive genotype 1a or 1b treated for 12 weeks, and (4) treatment-experienced genotype 1a or 1b (with failure to regimen that included boceprevir or telaprevir) treated for 12 weeks. The SVR12 rates were all very high in all treatment arms (ranging from 86 to 100%) regardless of genotype and regardless of genotype; the addition of ribavirin did not significantly impact the SVR rates.

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ATOMIC

This randomized, open-label phase 2 study investigated the effectiveness and length of therapy of sofosbuvir-containing regimens in treatment-naive, noncirrhotic patients with chronic hepatitis C genotype 1, 4, 5, or 6. A total of 316 patients were randomized to one of three cohorts to receive

either sofosbuvir plus peginterferon plus ribavirin for 12 weeks (Cohort A), sofosbuvir plus peginterferon plus ribavirin for 24 weeks (Cohort B), or sofosbuvir plus peginterferon plus ribavirin for 12 weeks, followed by an additional 12 weeks of either sofosbuvir or sofosbuvir plus ribavirin (Cohort C). In all cohorts, ribavirin was weight-based dosing. Most of the patients enrolled had HCV genotype 1 (94.9%), followed by genotype 4 (3.5%), and genotype 6 (1.6%). The SVR24 rates were similar in all three cohorts (A = 89%, B = 89%, and C = 87%). This study established the effectiveness of a 12-week course of sofosbuvir plus peginterferon plus ribavirin for 12 weeks in treatment-naive patients.

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BOSON

In the randomized, open-label BOSON trial, investigators enrolled patients with genotype 2 or 3 chronic HCV infection to receive one of three treatment regimens: sofosbuvir plus ribavirin for 16 weeks, sofosbuvir plus ribavirin for 24 weeks, and sofosbuvir plus ribavirin plus peginterferon alfa-2a for 12 weeks. All patients enrolled with genotype 2 were treatment-experienced and had cirrhosis whereas those with genotype 3 were either treatment-naive or treatment-experienced, with or without cirrhosis. Among the 592 patients enrolled in the study, 544 (92%) had genotype 3 infection and 48 (8%) had genotype 2. For the patients with genotype 3 infection, the SVR 12 rates were 71% with the 16-week sofosbuvir plus ribavirin regimen, 84% with 24 weeks of sofosbuvir plus ribavirin, and 93% with 12 weeks of sofosbuvir plus ribavirin plus peg interferon. The SVR12 findings in genotype 3 were similar for both treatment-naive and treatment-experienced patients, with both groups showing the best results with the 12-week regimen of sofosbuvir plus ribavirin plus peginterferon. For the patients with genotype 2 infection, the SVR 12 rates were 87% with the 16-week sofosbuvir plus ribavirin regimen, 100% with 24 weeks of sofosbuvir plus ribavirin, and 94% with 12 weeks of sofosbuvir plus ribavirin plus peginterferon.

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COSMOS

In this phase 2a, open-label trial, patients with chronic HCV genotype 1 infection were randomized to receive sofosbuvir plus simeprevir, with or without ribavirin, for either 12 or 24 weeks. The study included treatment-naive and treatment-experienced patients. The study design included two cohorts and the primary outcome was SVR12. Patients in cohort 1 consisted of 80 subjects with Metavir fibrosis stage F0-F2 and nonresponse to prior treatment with peginterferon plus ribavirin. Cohort 2 enrolled 87 patients with Metavir fibrosis stage F3-F4 who were either treatment naive or had a nonresponse to prior treatment with peginterferon plus ribavirin. The overall SVR rates were very high in both cohorts: 90% in cohort 1 and 94% in cohort 2. Extending therapy to 24 weeks did not clearly improve SVR rates, except possibly in patients with prior relapse and advanced fibrosis. Patients with a baseline G80K (Gln80Lys) polymorphism had high SVR rates, including those with compensated cirrhosis. Rapid virologic response did not predict SVR. Phase 3 trials are now underway with simeprevir plus sofosbuvir in the OPTIMIST program.

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Egyptian Ancestry Genotype 4

In this phase 2 trial conducted in the United States, investigators randomized treatment-naive and treatment-experienced patients of Egyptian ancestry with genotype 4 infection to receive either 12- or 24-weeks of sofosbuvir plus weight-based ribavirin. Investigators enrolled 60 patients and 32 (53%) of the 60 were treatment-experienced; among these treatment-experienced patients 20 (63%) of 32 had a history of prior nonresponse. For treatment-naive patients who received 24 weeks of therapy, 14 (100%) of 14 achieved an SVR12 and 11 (79%) of 14 treated with 12 weeks achieved an SVR12. Among the treatment-experienced patients treated for 24 weeks, 13 (87%) of 15 had an SVR12, compared with 10 (59%) of 17 in those treated for 12 weeks. For the treatment-experienced patients, the SVR12 data was not broken out for prior nonresponders verus relapsers. This study showed that 24 weeks of sofosbuvir plus ribavirin is effective for the treatment of genotype 4 HCV.

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ELECTRON: Arms 1-8

In this phase 2a ELECTRON substudy (arms 1 to 8 of the parent ELECTRON trial), investigators examined the efficacy of sofosbuvir with or without ribavirin and peginterferon in patients with genotype 1,2, or 3 chronic hepatitis C infection. Arms 1 to 6 in the trial involved treatment-naive patients with genotype 2 or 3 infection, arm 7 was treatment-experienced null responders with genotype 1, and arm 8 treatment-naive with genotype 1. Regimens included sofosbuvir alone, sofosbuvir plus ribavirin for 12 weeks, sofosbuvir plus ribavirin for 12 weeks in combination with peginterferon for 4 to 12 weeks, and an 8-week regimen of sofosbuvir plus ribavirin plus peginterferon. Most of the regimens perferformed extremely well, with 5 of the 8 regimens yielding an SVR rate of 100%. The sofobuvir monotherapy (SVR = 60% SVR) and sofosbuvir plus ribavirin in prior null responders (SVR = 10%) did not perform well.

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ELECTRON (Overview): Arms 1-22

The ELECTRON Study is a complex phase 2 trial comprised of 6 parts and 22 arms. The overarching goal of the ELECTRON trial is to examine sofosbuvir in combination with additional agents, including peginterferon, ribavirin, ledipasvir, and GS-9669. The trial has arms that include patients with genotype 1, 2, or 3. Treatment duration ranges from 6 to 12 weeks. Different published studies and abstracts have utilized a combination of arms in the ELECTRON study.

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FISSION

This randomized, open-label, phase 3 trial involved treatment-naïve patients with genotype 2 or 3 hepatitis C infection and demonstrated that overall a 12-week regimen of sofosbuvir plus weight-based ribavirin was non-inferior to the standard of care (24 weeks of peginterferon plus fixed-dose ribavirin). The sustained virologic response rate at 12 weeks post-treatment (SVR12) was 67% with combined data from both genotype 2 and 3. In the patients treated with sofosbuvir and ribavirin, the SVR12 rates were notably higher in patients with genotype 2 (97%) versus those with genotype 3 (57%). All treatment failure resulted from viral relapse. Safety and tolerability of the sofosbuvir combination was comparable to that of ribavirin. Although this study showed very good overall results with the all-oral therapy for treatment-naïve patients with genotype 2 or 3 infection, it clearly

signaled that 12 weeks of therapy with sofosbuvir plus ribavirin for genotype 3 infection is inadequate. This study was published in tandem with the NEUTRINO trial.

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FUSION

This randomized, double-blind, placebo-controlled, phase 3 trial involved treatment-experienced patients with genotype 2 or 3 chronic hepatitis C infection who received sofosbuvir plus weight-based ribavirin for 12 or 16 weeks. The SVR12 was 50% in the 12-week arm versus 73% in the 16-week arm. The subset of patients that appeared to benefit the most from a longer duration of therapy were those with genotype 3 infection (SVR achieved in 62% with 16 weeks versus 30% with 12 weeks) or cirrhosis (SVR 66% with 16 weeks versus 31% with 12 weeks). Sofosbuvir was well tolerated and treatment failure resulted from relapse with no cases of virologic breakthrough. Overall, this study in treatment-experienced patients showed excellent results with sofosbuvir and ribavirin in patients with genotype 2 infection, but the 12-week course of sofosbuvir and ribavirin performed poorly in patients with genotype 3 infection or cirrhosis. This study was published in tandem with the POSITRON trial.

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HCV Target: Renal Disease

In the HCV TARGET trial, investigators reported findings from a longitudinal cohort study of HCV treatment of 1893 patients, including patients renal disease, using one of four sofosbuvir-containing regimens: (1) sofosbuvir plus peginterferon plus ribavirin, (2) sofosbuvir plus ribavirin, (3) sofosbuvir plus simeprevir, and (4) sofosbuvir plus simeprevir plus ribavirin. Overall, the SVR12 rates were high (81 to 89%) across different levels of baseline renal insufficiency, with the one exception that cirrhotic patients with estimated GFR less than 30 mL/min/1.73m^2 had significantly lower SVR12 rates. In addition, the rate of treatment-related anemia was higher in patients with more advanced renal disease.

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LONESTAR-2

The LONESTAR-2 trial is an open-label, single arm, phase 2 trial involving retreatment of 47 patients with genotype 2 or 3 infection who previously failed treatment with peginterferon and ribavirin. All patients received a 12-week course of sofosbuvir plus peginterferon alfa-2a plus weight-based ribavirin. Patients with compensated cirrhosis were eligible for the trial and 55% of the patients enrolled had cirrhosis. Overall, 42 (89%) of 47 patients achieved an SVR12. Analyzed by genotype, an SVR12 was obtained in 22 (96%) of 23 patients with genotype 2 and in 20 (83%) 24 of patients with genotype 3. The SVR rates were similar in patients with or without cirrhosis. The adverse effect profile was similar to what would be expected with peginterferon and ribavirin alone, indicating that sofosbuvir was well tolerated.

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NEUTRINO

This open-label, single-arm, phase 3 trial in treatment-naive patients with chronic hepatitis C infection and genotypes 1, 4, 5 or 6 demonstrated very high SVR12 when treated with a 12-week course of sofosbuvir plus peginterferon plus weight-based ribavirin. Overall, 90% of the patients in the study achieved an SVR12 and all patient subgroups had an SVR12 of 80% or greater, including certain groups (black patients and patients with cirrhosis) that historically have low SVR rates. The regimen was generally well tolerated. All cases that did not achieve SVR12 were the result of viral relapse; viral resistance to sofosbuvir was not detected. This study was published in tandem with the FISSION trial.

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NIAID SPARE

This open-label, two-part, phase 2 trial study was performed by investigators at the National Institutes of Health (NIH) and investigators examined the efficacy of a 24-week treatment course with sofosbuvir plus weight-based ribavirin in treatment-naïve patients with genotype 1 chronic hepatitis C infection. This trial enrolled a high percentage of patients with traditionally unfavorable treatment characteristics: 83% were black, 81% had non-CC IL28B genotype, and 23% had F3-F4 stage liver disease by Knodell histology Activity Index (HAI) scoring. In the first part of the trial, investigators assigned 10 patients with early to moderate liver fibrosis to receive sofosbuvir plus weight-based ribavirin. Nine (90%) of the 10 patients achieved a sustained virologic response at week 24 post-treatment (SVR24). In part 2 of the study, 50 patients (with all stages of liver fibrosis) were randomized to receive either sofosbuvir plus weight-based ribavirin or sofosbuvir plus low-dose ribavirin. This study demonstrated relatively good results with all the oral regimen of sofobuvir plus ribavirin in very difficult to treat patients with hepatitis C. Patients receiving weight-based dosing of ribavirin had better SVR24 rates that with low-dose ribavirin (68% versus 48%, p=0.20.

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OPTIMIST-1

This randomized, phase 3, open-label trial compared an 8-week versus 12-week regimen of simeprevir plus sofosbuvir in treatment-naive and treatment-experienced patients with chronic HCV genotype 1. Patients with cirrhosis were excluded from the OPTIMIST-1 trial. Overall, SVR12 rates were better in patients in the 12-week arm (150 [97%] of 155) than in those in the 8-week arm (128 [83%] of 155). The superiority of the 12-week regimen compared with the 8-week regimen was observed in both treatment-naive (97% versus 85%) and treatment-experienced (95% versus 77%) patients. With the 12-week regimen, the SVR12 rates were greater than 95% in all of the following subgroups: genotype 1a, genotype 1a with the baseline Q80K mutation, genotype 1a without the baseline Q80K mutation, and genotype 1b. The 8-week regimen performed particularly poorly in patients with genotype 1a with the baseline Q80K mutation (SVR12 of 73%). Serious adverse effects occurred in only 1% of the study participants and these adverse effects were not attributable to simeprevir or sofosbuvir. This study demonstrates the all-oral 12-week regimen of simeprevir plus sofosbuvir is highly effective and well toleratedin treatment-naive and treatment-experienced HCV genotype 1 patients without cirrhosis.

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OPTIMIST-2

This randomized, phase 3, open-label, single-arm trial examined the effectiveness and safety of a 12-week treatment course with simeprevir plus sofosbuvir in treatment-naive or treatment experienced patients with chronic HCV genotype 1 and compensated cirrhosis. Overall, treatment with simeprevir plus sofosbuvir resulted in an SVR12 in 86 (83%) of 103 patients. Treatment-naive patients had better SVR12 rates than the treatment experienced patients (88% versus 79%). In the genotype 1a patients, the SVR12 rates were higher in the group without the baseline Q80K mutation than those with the baseline Q80K mutation (92% versus 74%). Serious adverse effects occurred in only 1% of the study participants and these adverse effects were not attributable to simeprevir or sofosbuvir. This study demonstrated an all-oral 12-week regimen of simeprevir plus sofosbuvir is generally effective in treatment-naive and treatment-experienced patients with cirrhosis and HCV genotype 1 infection, with the exception that patients with genotype 1a and the baseline Q80K mutation have SVR rates of only 74%.

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PHOTON-1

This open label, nonrandomized, uncontrolled, phase 3 trial evaluated 223 patients with chronic hepatitis C genotypes 1, 2, or 3 and HIV coinfection. This trial examined the efficacy of the all-oral regimen of sofosbuvir plus ribavirin (weight-based) in treatment-naive and treatment-experienced patients. Patients in the trial were required to be on stable antiretroviral therapy with an undetectable HIV RNA level and CD4 count greater than 200 cells/mm^3, or if untreated, they had CD4 count greater than 500 cells/mm^3. The trial included treatment-naive patients with genotype 1, 2, or 3 and treatment-experienced patients with genotype 2 or 3. A 24-week treatment course was given to all patients with HCV genotype 1 and to treatment-experienced patients with HCV genotype 2 or 3; treatment-naive patients with HCV genotype 2 or 3 received a 12-week treatment course. Patients with cirrhosis were included in the trial, but could not comprise more than 20% of the total number of subjects enrolled. For treatment-naive patients, the SVR12 rates were 76% with genotype 1, 88% with genotype 2, and 67% with genotype 3. Treatment-experienced patients with genotype 2 had a 92% SVR12 rate and those with genotype 3 had a 94% SVR12 rate. This study demonstrated that patients coinfected with HIV can achieve excellent SVR rates with the all-oral regimen of sofosbuvir and ribavirin. In addition, the study showed the clear benefit of extending treatment with sofosbuvir plus ribavirin from 12 to 24 weeks in patients with genotype 3 HCV infection.

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PHOTON-2

In this open-label, phase 3 trial, 274 HIV-infected patients coinfected with HCV genotype 1, 2, 3, or 4 received treatment with the all-oral regimen of sofosbuvir plus weight-based ribavirin. The study enrolled treatment-naive patients with genotypes 1, 2, 3, or 4 and treatment-experienced with genotype 2 or 3. A 24-week treatment course was given to all patients with HCV genotype 1, 3, or 4 and treatment-experienced patients with genotype 2, whereas treatment-naïve with HCV genotype 2 received 12 weeks. Among those enrolled, 81% of the patients were HCV treatment naïve and 20% had cirrhosis. The mean CD4 count was 588 cells/mm^3 and 97% were on antiretroviral therapy (tenofovir-emtricitabine plus one of the following: efavirenz, atazanavir plus ritonavir, darunavir plus ritonavir, rilpivirine, or raltegravir). The SVR12 rates were high with all HCV genotypes: GT1 (85%), GT2 (88%), GT3 (89%), and GT4 (84%). In addition, the treatment responses were similar in the treatment-naïve and treatment-experienced patients.

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POSITRON

This randomized, double-blind, placebo-controlled, phase 3 trial enrolled patients with genotype 2 or 3 hepatitis C infection considered unable to receive peginterferon-based therapy (intolerant with prior treatment, unwilling, or ineligible to receive). Most (82%) had not received prior interferon therapy. Patients were randomized to receive either 12 weeks of placebo control or sofosbuvir plus weight-based ribavirin. The overall sustained virologic response rate at 12 weeks post-treatment (SVR12) was 78% in the sofosbuvir plus ribavirin arm. As demonstrated in other sofosbuvir trials, the SVR12 rate was higher for patients with genotype 2 (93%) than genotype 3 (61%). All treatment failures were the result of viral relapse. The combination of sofosbuvir and ribavirin was well tolerated with a very low rate of discontinuation due to adverse effects. This trial demonstrated excellent response rates to a 12-week course of sofosbuvir plus ribavirin in patients with genotype 2 infection, but relatively poor responses with this regimen in patients with genotype 3 infection. This study was published in tandem with the FUSION trial.

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PROTON

This phase 2 trial investigated sofosbuvir plus peginterferon and ribavirin in patients with genotypes 1-3. The study included two cohorts: (Cohort A consisted of 122 patients with genotype 1 and Cohort B included 25 patients with genotype 2 or 3 infection. In the Cohort A cohort, patients received a 12-week course of sofosbuvir at either 200 mg or 400 mg once daily combined with peginterferon and ribavirin, with an additional 12- or 24 weeks of peginterferon and ribavirin. In addition, one group of patients in Cohort A received 48 weeks of peginterferon and ribavivin, without sofosbuvir. All patients in Cohort B received a 12-week course of sosbuvir 400 mg once daily combined with peginterferon and ribavirin. Patients with genotype 1 (Cohort A) had very high SVR24 rates if they received the triple therapy regimen of sofosbuvir plus peginterferon and ribavirin (90% in the sofosbuvir 200 mg dose and 91% in the sofosbuvir 400 mg arm), which were much higher than the SVR24 rate of 58% in the arm that received peginterferon and ribavirin. In Cohort B (genotype 2 or 3), the SVR24 rate was 92%. Adverse effects were consistent with those associated with peginterferon and ribavirin.

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QUANTUM

The QUANTUM trial is a randomized phase 2b trial that examined various combinations of sofosbuvir, weight-based ribavirin, and the investigational agent GS-0938 (nucleotide NS5B polymerase inhibitor) in hepatitis C treatment-naive patients. A total of 235 patients enrolled in the study, with the percentage of patients with genotype 1 ranging from 73 to 79% in the treatment arms. Due to unexpected major increases in aminotransferase levels in patients receiving GS-0938, the study protocol was modified and all GS-0938 arms were halted. In addition, patients in a GS-0938 arm who did not achieve SVR12 were retreated with 24 weeks of sofosbuvir and ribavirin. Overall, among patients treated with sofosbuvir plus ribavirin, the SVR12 rates were 56% in the 12-week course, 52% in the 24-week course, and 70% in the retreatment 24-week course. When examining response rates only for genotype 1a and 1b infections, the SVR12 rates for these genotypes were similar to

the overall SVR rates, with the exception that patients with genotype 1b who received retreatment had only a 48% SVR rate.

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Retreatment of Sofosbuvir Failure

In this open-label study, investigators enrolled patients with genotype 2 or 3 chronic HCV infection who previously failed a sofosbuvir-containing regimen in a prior clinical trial (FISSION, POSITRON, or FUSION). Among the 107 patients enrolled in the study, 96 had genotype 3 infection and 11 had genotype 2. The retreatment for patients in the study consisted of a 12-week course of sofobuvir plus peginterferon plus ribavirin (34 patients enrolled) or a 24-week course of sofosbuvir plus ribavirin (73 patients enrolled). Overall, for patients who had thus far completed treatment, 24 (92%) of 26 who received sofosbuvir plus peginterferon plus ribavirin achieved an SVR12, compared with 25 (63%) of 40 who received 24 weeks of sofosbuvir plus ribavirin.

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Sofosbuvir for Genotype 1-4 in HIV Coinfection

In this phase 2, single-arm, single-site, open-label trial, 23 HCV treatment-naïve patients with genotypes 1-4 and HIV coinfection received a 12-week course of peginterferon alfa-2a, ribavirin (weight-based), and sofosbuvir. Patients were required to have a CD4 count greater than 200 cells/mm^3 and to be on stable antiretroviral therapy for at least 8 weeks. The mean CD4 count was 562 cells/mm^3; all patients were receiving a tenofovir-emtricitabine backbone plus efavirenz, atazanavir plus ritonavir, darunavir plus ritonavir, rilpivirine, or raltegravir. Among the patients enrolled 19 (83%) of 23 had HCV genotype 1. The overall SVR12 rate was 21 (91%) of 23. Among the patients with genotype 1 infection, 17 (89%) of 19 achieved an SVR12. The SVR12 rates related to antiretroviral therapy showed 93% with protease inhibitors, 91% with non-nucleoside reverse transcriptase inhibitors, and 100% with integrase strand transfer inhibitors (raltegravir). For the two patients who did not achieve SVR, both had genotype 1a infection and one of these patients stopped therapy after only 6 weeks.

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Sofosbuvir for HCV Recurrence Following Liver Transplantation

This phase 2 trial examined the efficacy of a 24-week course of sofosbuvir plus ribavirin for patients with HCV recurrence following liver transplantation. The ribavirin was dosed starting at 400 mg per day and increased up to 1200 mg/day based on weight and on tolerance (hemoglobin and creatinine clearance). A total of 40 patients enrolled, 88% had received previous HCV therapy, 40% had biopsy confirmed cirrhosis, and the median time since liver transplantation was 4.3 years. All 40 patients had an undetectable HCV RNA at the end of treatment and indicated that 28 (70%) of 40 patients achieved an SVR12. The regimen of sofosbuvir plus ribavirin was relatively well-tolerated, but 20% of the subjects developed anemia. This study, although involving a small number of subjects, has generated encouraging data for the the use of sofosbuvir plus ribavirin in the post-liver transplantation setting.

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Sofosbuvir to Prevent Post-Transplant HCV Recurrence

This open-label, phase 2 trial, multicenter trial enrolled 63 patients with chronic hepatitis C and compensated cirrhosis awaiting liver transplantation for hepatocellular cancer. Patients receive sofosbuvir plus ribavirin for up to 48 weeks while awaiting transplant (all patients received at least 12 weeks of therapy). Among the 61 treated patients, 46 underwent liver transplantation; the study analysis was performed on the 43 (93%) of 46 patients who underwent transplant and had an HCV RNA level less than 25 IU/ml at the time of transplant. The sofosbuvir plus ribavirin was discontinued approximately 24 hours prior to transplantation. At 12 weeks post-transplantation, 30 (70%) of 43 patients had undetectable HCV RNA levels. Overall, the treatment was well-tolerated and the most frequently reported adverse effects were faigure, headache, and anemia.

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VALENCE

This randomized, phase 3 trial examined the effectiveness of sofosbuvir plus weight-based ribavirin in treatment-naïve or experienced patients with genotype 2 or 3 chronic hepatitis C infection. The original protocol design had patients randomized to receive placebo or 12 weeks of therapy with sofosbuvir plus weight-based ribavirin. After knowledge evolved regarding poor responses to 12 weeks of therapy in patients with genotype 3, the protocol was amended so that patients with genotype 3 received 24 weeks of therapy. In addition, the placebo arm was modified so that patients could receive an alternative protocol. Investigators enrolled and treated 419 patients: 91 with genotype 2 infection and 328 with genotype 3 infection. Among those enrolled in the study, 21% had cirrhosis and 58% had undergone previous treatment with an interferon-based therapy. For patients with genotype 2 infection, an SVR12 was achieved in 68 (93%) of 73 patients. Among those with genotype 3 who received 24 weeks of therapy, SVR12 was met in 213 (85%) of 250 patients and the responses were clearly better in patients without cirrhosis than those with cirrhosis (91% versus 68%). Of note, among the genotype 3 patients treated with 12 weeks of therapy, only 3 (27%) of 11 had an SVR12.

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Figures

Figure 1 Sofosbuvir (*Sovaldi*) Pill Bottle

Photo: Andrew Karpenko, University of Washington

Figure 2 Sofosbuvir (*Sovaldi*) Pill

Photo: Andrew Karpenko, University of Washington