

Brand Name: Sovaldi™

Generic Name: sofosbuvir

Manufacturer³: Gilead Sciences Inc.

Drug Class^{1,2}: Antiinfective, Antihepaciviral, Anti-HCV, NS5B polymerase inhibitor

Uses:

Labeled^{1,2,3,4,5}: Chronic hepatitis C treatment of genotype 1, 2, 3, or 4 in combination with ribavirin OR with peginterferon alfa and ribavirin, including patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 coinfection

Mechanism of action^{1,2,3,4,5}: Intracellular metabolism converts the nucleotide prodrug sofosbuvir into the pharmacologically active uridine analog triphosphate (GS-461203). The active metabolite is then incorporated into HCV RNA via the NS5B polymerase where it acts as a chain terminator and inhibits HSV NS5B RNA-dependent RNA polymerase which is essential for viral replication.

Pharmacokinetics^{1,2,3,4,5}:

T _{max}	Parent drug: 0.5-2 hours Major metabolite (GS-331007): 2-4 hours
V _d	Not reported
t _½	Parent drug: 0.4 hours Major metabolite (GS-331007): 27 hours
Clearance	Not reported
Protein binding	~61% to 65% bound to human plasma proteins
Bioavailability	Not reported

Metabolism: Sofosbuvir is extensively hepatically metabolized and forms pharmacologically active nucleoside (uridine) analog triphosphate GS-461203; dephosphorylation results in the formation of nucleoside inactive metabolite GS-331007. Neither CYP450 enzymes nor glutathione are involved in its metabolism.

Elimination: Sofosbuvir is primarily excreted (80%) through the kidneys into urine (78% as GS-331007 and 3.5% as sofosbuvir) and through the feces (14%).

Efficacy:

Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 May 16;368(20):1878-87.

Study design: Phase 3, single-group, multicenter, open-label study design (NEUTRINO trial)

Description of study: *Methods:* A total of 327 patients infected with HCV genotype 1, 4, 5, or 6 at 56 sites in the United States were enrolled in this study of sofosbuvir plus

peginterferon/ribavirin. Patients included in the study reflected a distribution of genotypes that is consistent with the prevalence of genotypes in the United States (89% genotype 1, 9% genotype 4, 2% genotype 5 or 6.) All patients received 12 weeks of treatment with oral sofosbuvir 400 mg once daily, oral weight-based ribavirin (100mg daily in patient with a body weight of <75 kg and 1200 mg daily in patients with a body weight of ≥75 kg), and once weekly subcutaneous peginterferon alfa-2a 180 µg. Initial screening assessments included standard clinical laboratory testing, measurement of serum HCV RNA levels, and *IL28B* genotyping testing. Assessments throughout treatment included standard laboratory tests, measurement of serum HCV RNA levels, measurement of vital signs, electrocardiography, and symptom-directed physical examinations. Resistance testing was performed in patients receiving sofosbuvir who did not have virologic response. The primary efficacy endpoint of this study was sustained virologic response (SVR), defined as an HCV RNA level below the lower limit of quantification, at 12 weeks after the end of treatment. Power was set at 90% with at least 300 patients enrolled to show a rate of sustained virologic response with the sofosbuvir regimen that was higher than 60%. *Outcome results:* A total of 295 of the 327 patients (90%; 95% CI 97 to 93) had a sustained virologic response 12 weeks after treatment, and rates of sustained virologic response did not differ greatly according to genotype (89% genotype 1, 96% genotype 4, and all patients with genotype 5 and 6.) Twenty-eight patients had a relapse after virologic response at the end of treatment, but none had resistance-associated variants. With regard to safety, only 5 patients (2%) discontinued treatment due to an adverse event, but 310 (95%) of patients did experience any adverse event; most commonly, fatigue, headache, nausea, and insomnia.

Limitations: This study only looked at a single-group, and did not utilize a placebo or a standard treatment group receiving just peginterferon/ribavirin group for comparison, so it is difficult to assess if the treatment effect observed was due to just sofosbuvir. Patients were primarily white (69%) and genotype 1a. Although genotype 1a is the most prevalent in the United States, the study did not cover all genotypes, limiting the generalizability to others.. The study also did not utilize more than one combination of sofosbuvir/peginterferon/ribavirin combined in a different manner other than including all three, making it difficult to determine if the same results could be achieved in a population where only a two-drug combination was used. The trial was supported by the manufacturer, Gilead Sciences, and employees of Gilead Sciences conducted the study, resistance analysis, statistical analysis, study-team leadership, and provided medical writing support. The study only evaluated those patients who relapsed at the end of treatment for resistance-associated mutations which showed no patients having such mutations, so it is unknown from this study was outcomes may be in an individual with a resistance-associated mutation(s).

Conclusion: In this open-label single-group study of sofosbuvir, peginterferon, and ribavirin in previously untreated patients with HCV infection, 90% of the patients met the primary endpoint of a sustained virologic response at 12 weeks. In particular, patients with HCV genotype 1 or 4 infection displayed high efficacy. It is important to note that the overall response rates shown within this study were high even with the study population containing patients with characteristics that have historically been associated with lower rates of response to treatment (i.e. cirrhosis, a high baseline viral load, black race, and a non-CC *IL28B* genotype.) However more studies need to be conducted that compare the treatment regimen to other treatment modalities, duration of treatment, as well as a different antiviral combination regimen.

Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med.* 2013 May 16;368(2):1867-77.*

Study Design: Multicenter, randomized, blinded, placebo-controlled study (POSITRON trial)

Description of study: *Methods:* This study compared 12 weeks of treatment with sofosbuvir (400 mg once daily) and ribavirin (weight-based; 1000mg <75kg once daily, 1200mg ≥75kg once daily) with matching placebo in 278 patients with HCV genotype 2 or 3 who had previously discontinued interferon therapy owing to unacceptable adverse events, who had a concurrent medical condition precluding therapy with an interferon-containing regimen, or who had decided against treatment with an interferon-containing regimen, but prior treatment failure with an interferon-based regimen was not a reason for exclusion. Patients were stratified based on the presence (up to 20% of patients enrolled) or absence of cirrhosis, randomized, and enrolled in 63 sites in the United States, Canada, Australia, and New Zealand. Screening assessments included standard laboratory testing, measurement of the serum HCV RNA level, and *IL28B* genotyping. Assessments during treatment included standard laboratory testing, measurement of serum HCV RNA level, assessment of vital signs, and symptom-directed physical examination with all adverse events recorded and graded. Resistance testing was performed in patients receiving sofosbuvir who did not have virologic response. A sample of 180 patients in the sofosbuvir group and 60 in the placebo group was determined to provide 99% power to detect a between-group difference in the rate of SVR of 40% with 0.05 level of significance. *Outcome results:* The distribution of patients on the basis of classification that interferon therapy was not an option was similar between the treatment and placebo groups. In this population with interferon not as an option, the rate of SVR at 12 weeks after treatment was 78% (95% CI, 72 to 83) in the sofosbuvir/ribavirin treatment group as compared to placebo. Of the 153 patients who could be evaluated, none had a virologic relapse after week 12. Logistic-regression analysis showed HCV genotype 3 having a significant association with reduced rates of SVR compared to HVC genotype 2, with 61% of patients vs 93% having a SVR in each group, respectively. With regard to cirrhosis, 81% of patients without vs 61% of those with had an SVR in those who received sofosbuvir and ribavirin. No patient who received sofosbuvir had a virologic breakthrough or a failure to have a response to treatment and 42 patients had a relapse after treatment, but analysis showed no resistance-associated variants. Four patients who received sofosbuvir/ribavirin vs three who received placebo discontinued treatment, with rates of serious adverse events corresponding at 5% vs 3% in each respective group. As expected, higher rates of fatigue, insomnia, and anemia were seen in the sofosbuvir/ribavirin group.

Limitations: The study included patients who had previously been treated with interferon and also those patients who chose not to receive an interferon-containing regimen. It is unknown whether or not there was an impact on the outcomes found in this study in those patients who had received interferon in the past (i.e. possible resistance mutations developed from past therapy.) Patients included were primarily white and there was a large discrepancy in the number of patients included in the placebo vs treatment arm (71 vs 207) complicating a true comparison, with only 20% of patients completing treatment vs 50% who did not. Placebo may have also not been the most ethical control treatment, and the standard peg-interferon/ribavirin may have been a better control treatment option. The trial was sponsored, designed, and conducted by the manufacturer of sofosbuvir, Gilead Sciences, in collaboration with the principal investigators. The sponsor also collected the data, monitored study conduct,

and performed the statistical analyses. The study only evaluated those patients who relapsed at the end of treatment for resistance-associated mutations which showed no patients having such mutations, so it is unknown from this study what outcomes may be in an individual with a resistance-associated mutation(s).

Conclusion: In this randomized, multi-center, blinded study of 12 weeks sofosbuvir/ribavirin vs placebo, the findings suggest that 12 weeks of treatment with sofosbuvir and ribavirin can be an effective option in patients with HCV genotype 2. Response rates among patients with HCV genotype 3 infection were lower than the rates among those with HCV genotype 2 infection, especially in the subgroup of patients with cirrhosis. In patients with HCV genotype 3, 12 weeks of treatment with sofosbuvir and ribavirin may not provide an adequate treatment to achieve goal SVR, and extending the duration of therapy to 16 weeks, additional immune modulation, or a more potent antiviral suppression given for 12 weeks to enhance virologic clearance may be preferable.

Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013 May 16;368(2):1867-77.*

Study design: Multi-center, randomized, blinded, active-control study (FUSION trial)

Description of study: *Methods:* This study enrolled patients who had not had a response to prior treatment with an interferon-containing regimen with HCV genotype 2 or 3 with or without cirrhosis from 67 sites in the United States, Canada, and New Zealand who were then randomized in a 1:1 ratio of two treatment groups: 12 weeks of sofosbuvir and ribavirin followed by 4 weeks of matching placebo OR 16 weeks sofosbuvir and ribavirin. Screening assessments included standard laboratory testing, measurement of the serum HCV RNA level, and IL28B genotyping. Assessments during treatment included standard laboratory testing, measurement of serum HCV RNA level, assessment of vital signs, and symptom-directed physical examination with all adverse events recorded and graded. Resistance testing was performed in patients receiving sofosbuvir who did not have virologic response. *Outcome results:* It was determined that a sample of 100 patients in each group would provide more than 97% power to detect an improvement of at least 20% in the rate of an SVR and would provide 82% power to detect a difference of 20% in response rates between the 12-week and 16-week treatment groups. For this study, 202 patients underwent randomization with 201 patients who began treatment with balanced baseline/demographic characteristics. Approximately 34% of patients had cirrhosis which was associated with a decreased rate of sustained virologic response, particularly among patients with HCV genotype 3 infection who received 12 weeks of treatment. Sixty-three percent of patients were infected with genotype 3 HCV which was significantly associated with a lower response rate with both 12 and 16 weeks of treatment. The rates of SVR were 50% (95% CI, 40 to 60) for the 12-week group and 73% (95% CI, 63 to 81) in the 16-week group ($p < 0.001$ for both.) Patients receiving 16 weeks of treatment had a significantly higher SVR rate than patients receiving 12 weeks of treatment. (-23% difference, 95% CI, -35 to -11, $p < 0.001$.) No patient who received sofosbuvir had a virologic breakthrough or a failure to have a response to treatment and 73 patients had a relapse after treatment, but analysis showed no resistance-associated variants. One patient in the 12-week group discontinued treatment during the 4-week placebo phase of dosing, and rates of serious adverse events were 5% in the 12-week group and 3% in the 16-week group.

Limitations: The study included patients who had previously been treated with interferon, so it is unknown whether or not there was an impact on the outcomes found in this study because of this (i.e. possible resistance mutations developed from past therapy.) The 16-week treatment arm had only 27% of patients actually complete treatment vs 46% in the 12-week and the 16-week arm of 95 patients did not meet power which required 100 patients. Additionally, the study wanted to aim for a power that would result in a 20% SVR which is much lower than what would be clinically significant, making the power very high for this measure. The trial was sponsored, designed, and conducted by the manufacturer of sofosbuvir, Gilead Sciences, in collaboration with the principal investigators. The sponsor also collected the data, monitored study conduct, and performed the statistical analyses. Genotype 2 and 3 were the only specific ones used in this study, so it would be difficult to extrapolate these results to the other HCV genotypes when debating if extended therapy would benefit a patient. The study only evaluated those patients who relapsed at the end of treatment for resistance-associated mutations which showed no patients having such mutations, so it is unknown from this study what outcomes may be in an individual with a resistance-associated mutation(s)."

Conclusion: In this randomized, multi-center, blinded active-control study of 12 weeks of sofosbuvir and ribavirin followed by 4 weeks of matching placebo OR 16 weeks sofosbuvir and ribavirin, the findings suggest that an extended duration of therapy 16 weeks of treatment with sofosbuvir and ribavirin can be an effective option in patients with HCV genotype 2. Response rates among patients with HCV genotype 3 infection were lower than the rates among those with HCV genotype 2 infection, especially in the subgroup of patients with cirrhosis. In patients with HCV genotype 3, 12 weeks of treatment with sofosbuvir and ribavirin may not provide an adequate treatment to achieve goal SVR, and extending the duration of therapy, additional immune modulation, or a more potent antiviral suppression given for 12 weeks to enhance virologic clearance may be preferable.

Contraindications^{1,2,3,4,5}: Combination treatment with sofosbuvir with ribavirin or peginterferon alfa/ribavirin is contraindicated in women who may become or who are pregnant and men whose female partners are pregnant due to the risk of birth defects and fetal death association with ribavirin. Sofosbuvir is pregnancy risk category B if administered alone, but pregnancy risk category X when used in combination. Because sofosbuvir is used as part of a combination antiviral therapy with peginterferon alfa and ribavirin, the contraindications applicable to these agents are also applicable.

Precautions^{1,2,3,4,5}:

Drug-drug interactions: Significant interactions, requiring dose or frequency adjustment, additional monitoring, and/or selection of an alternative agent include the use with potent P-GP inducers in the intestines

Pregnancy: Birth defects and/or fetal death may occur with ribavirin use; obtain a negative pregnancy test immediately before therapy containing ribavirin, monthly during therapy, and for at least 6-months after therapy is completed. The use of two non-hormonal forms of contraception is recommended during therapy and for at least 6 months after completion.

Lactation: It is unknown if sofosbuvir and its active metabolites are excreted into breast milk. A decision must be made whether to discontinue nursing or discontinue treatment with ribavirin-containing regimens due to the potential for adverse reactions.

Renal impairment: No adjustment is required in patients with mild or moderate renal impairment. Safety and efficacy of sofosbuvir have not been established in patients with severe renal impairment or end stage renal failure.

Hepatic Disease: No adjustment is required for patients with mild, moderate, or severe hepatic impairment. Safety and efficacy of sofosbuvir have not been established in patients with decompensated hepatic disease or decompensated cirrhosis.

Pediatric Use: Safety and effectiveness of sofosbuvir in children less than 18 years of age have not been established.

Geriatric Use: No dose adjustment is warranted in geriatric patients as response rates in clinical studies were similar to that of younger subjects across treatment groups.

Monotherapy or dose reduction of sofosbuvir is not recommended.

Adverse effects:

Occurring in >10% of patients

Central nervous system:

Fatigue (30% to 59%), headache (24% to 36%), insomnia (15% to 25%), chills (2% to 17%), irritability (10% to 13%)

Dermatologic:

Pruritus (11% to 27%), skin rash (8% to 18%)

Gastrointestinal:

Nausea (22% to 34%), decreased appetite (18%), diarrhea (9% to 12%)

Hematologic & oncologic:

Decreased hemoglobin (<10 g/dL: 6% to 23%; <8.5 g/dL: ≤2%), anemia (6% to 21%), neutropenia (<1% [interferon-free regimen] to 17% [interferon-containing regimen]), decreased neutrophils (≥0.5 to <0.75 times 10⁹/L: <1% [interferon-free regimen] to 15%; <0.5 times 10⁹/L: ≤5%)

Neuromuscular & skeletal:

Weakness (5% to 21%), myalgia (6% to 14%)

Respiratory:

Flu-like symptoms (6% to 16%)

Miscellaneous:

Fever (4% to 18%)

Occurring in 1% to 10% of patients

Gastrointestinal:

Increased serum lipase (>3 times ULN: ≤2%)

Hematologic & oncologic:

Thrombocytopenia (≤1%)

Hepatic:

Increased serum bilirubin (>2.5 times ULN: 3%)

Renal:

Increased creatine kinase (≥10 times ULN: 1% to 2%)

Occurring in <1% of patients, but with clinical implications

Hematologic effects:

Pancytopenia (particularly in subjects receiving concomitant pegylated interferon)

Psychiatric disorders:

Severe depression including suicidal ideation and suicide (particularly in subjects with pre-existing history of psychiatric illness.)

Drug interactions^{1,2,3,4,5:}

Potent inducers of intestinal P-glycoprotein

[Rifampin, St. John's Wort (*Hypericum perforatum*)]

May decrease the serum concentration of sofosbuvir and GS-331007, potentially resulting in the loss of antiviral efficacy.

Inducers of P-glycoprotein

[Carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone, tipranavir boosted with ritonavir, rifapentine, rifabutin]

May decrease the serum concentration of sofosbuvir and GS-331007, potentially resulting in the loss of antiviral efficacy.

Inhibitors of P-glycoprotein

May increase the serum concentration of P-glycoprotein.

Oxcarbazepine

May decrease the serum concentration of sofosbuvir and GS-331007, potentially resulting in the loss of antiviral efficacy.

Dosing/administration^{1,2,3,4,5:}

Adult Dosing

Chronic hepatitis C (CHC): Oral: 400 mg daily with concomitant ribavirin and with or without peginterferon alfa (maximum: 400 mg daily)

Treatment regimen and duration based on HCV genotype and/or clinical scenario:

Genotype 1

400 mg once daily + peginterferon alfa + ribavirin for 12 weeks

Patients who cannot receive interferon: 400 mg once daily + ribavirin for 24 weeks

Genotype 2

400 mg once daily + ribavirin for 12 weeks

Genotype 3

400 mg once daily + ribavirin for 24 weeks

Genotype 4

400 mg once daily + peginterferon alfa + ribavirin for 12 weeks

Hepatocellular carcinoma awaiting liver transplantation

400 mg once daily + ribavirin for 48 weeks or until the time of liver transplant, whichever occurs first

Pediatrics

Safety and efficacy of sofosbuvir have not been established in pediatric patients.

Geriatrics

Refer to adult dosing

Renal impairment

Specific guideline for dosage adjustments in renal impairment are not available; it appears no dosage adjustments are needed for mild or moderate renal impairment. Safety and efficacy have not been established in patients with severe renal impairment (eGFR < 30 ml/min) or end stage renal disease requiring hemodialysis.

Hepatic impairment

Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed. Safety and efficacy have not been established in patients with decompensated liver disease.

Sofosbuvir must not be dose reduced and it should be taken on a regular dosing schedule.

Sofosbuvir may be administered without regard to food.

Do not use sofosbuvir as monotherapy; use only in combination with ribavirin or in combination with pegylated interferon and ribavirin.

If the other agents used in combination with sofosbuvir are permanently discontinued, sofosbuvir should also be discontinued.

Use in special circumstances:

Overdosage³: The highest documented dose of sofosbuvir was a single suprathreshold dose of 1200mg administered to 59 healthy subjects. No untoward effects were observed at this dose and the adverse events were similar in frequency and severity to those reported in the placebo and sofosbuvir 400 mg treatment groups, but the effects of higher doses are not known. No specific antidote is available for overdose with sofosbuvir and general supportive measures are recommended. A 4-hour hemodialysis session removed 18% of the administered dose.

Conclusion:

Sovaldi™ (sofosbuvir) is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen with ribavirin OR with peginterferon alfa and ribavirin. Sovaldi™ efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection. Sovaldi™ is the first drug that has demonstrated safety and efficacy to treat certain types of HCV infection without the need for co-administration of interferon, providing a promising therapy option in those patients who may have failed or who are intolerant of previous treatment with an interferon containing regimen. Monotherapy with Sovaldi™ is not recommended as the development of resistance is rapid, and the individual combination treatment regimen and duration are dependent on both viral genotype and patient population. Treatment response varies based on baseline host and viral factors. The most significant warning/contraindication is that because ribavirin may cause birth defects and fetal death, Sovaldi™ in combination with peginterferon alfa/ribavirin or ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant. Although there are few drug

interactions as compared to other agents, drugs that are potent intestinal P-glycoprotein inducers should be avoided. The most common side effects reported in clinical trial subjects treated with Sovaldi™ and ribavirin were fatigue and headache. In participants treated with Sovaldi™ in combination with ribavirin and peginterferon-alfa, the most common side effects reported were fatigue, headache, nausea, insomnia and anemia. Due to its relatively minimal additive side effect profile, few drug interactions, option of combination with or without peg-interferon alfa, and wide applicability to most HCV genotypes with or without complication, Sovaldi™ addresses many unmet medical needs in these populations.

Recommended References:

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5. Sofosbuvir Oral. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: <http://online.factsandcomparisons.com>. Accessed: February 19, 2014.
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7. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013 May 16;368(2):1867-77.

Prepared by: Victoria Capozzi, Doctor of Pharmacy Candidate