Formulary Drug Reviews

Simeprevir Capsules

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Generic Name:	Simeprevir Capsules
Proprietary Name:	Olysio (Janssen Research)
Approval Rating:	1P (New Molecular Entity; Priority Review)
Therapeutic Class:	Antiviral Agents
Similar Drugs:	Boceprevir, Sofosbuvir, Telaprevir
Sound- or Look-Alike Names:	<i>Semprevir</i>

INDICATIONS

Simeprevir is indicated for use in combination with peginterferon alfa and ribavirin in the treatment of chronic hepatitis C virus (HCV) genotype 1 in adult patients with compensated liver disease, including cirrhosis. Screening patients with HCV genotype 1a for the presence of virus with the NS3 Q80K

polymorphism at baseline is strongly recommended; alternative therapy should be considered for patients who have the virus with this polymorphism, because simeprevir efficacy in combination with peginterferon alfa and ribavirin is substantially reduced in this population.¹ **Table 1** compares the US Food and Drug Administration (FDA)-approved indications for HCV antiviral agents.¹⁻⁴

CLINICAL PHARMACOLOGY

Simeprevir is an HCV NS3/4A protease inhibitor. Simeprevir produces a rapid reduction in plasma HCV RNA levels. Within days, there is a steep reduction of HCV RNA, followed by a more gradual decline. The median maximal reduction was 3.9 log₁₀ units/mL and occurred at a median of 6 days.⁵ Simeprevir has activity as a monotherapy against HCV genotypes 1, 2, 4, 5, and 6. It is not effective against HCV genotype 3.⁶⁻⁸ Reduced susceptibility has been observed in HCV carrying amino acid substitutions at NS3 positions F43, Q80, R155, A156, and/or D168; substitutions at D168V or A and R155K displayed the greatest

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Table 1. Comparison of the FDA-approved indications for HCV antiviral agents¹⁻⁴

	Simeprevir	Boceprevir	Sofosbuvir	Telaprevir
Brand name	<i>Olysio</i>	<i>Victrelis</i>	<i>Sovaldi</i>	<i>Incivek</i>
Manufacturer	Janssen	Merck	Gilead Sciences	Vertex Pharmaceuticals
Approval date	November 22, 2013	May 13, 2011	December 6, 2013	May 23, 2011
Indication	Chronic HCV genotype 1 infection in adult patients with compensated liver disease, including cirrhosis ^a	Chronic HCV genotype 1 infection in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have failed previous therapy with interferon and ribavirin, including prior null responders, partial responders, and relapsers	Treatment of chronic hepatitis C as a component of a combination antiviral treatment regimen; efficacy 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 coinfection	Chronic HCV genotype 1 infection in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have failed previous therapy with interferon-based treatment, including prior null responders, partial responders, and relapsers

Note: FDA = US Food and Drug Administration; HCV = hepatitis C virus.

^aSimeprevir has been studied in treatment-naïve patients and patients who have failed previous therapy with peginterferon and ribavirin, and the FDA-approved labeling contains dosing recommendations for patients who are treatment-naïve or who have failed previous therapy with interferon and ribavirin, including prior null responders, partial responders, and relapsers; although, these populations are not specified in the indication.

reductions in susceptibility, whereas Q80K or R, S122R, and D168E substitutions were associated with lesser reductions in susceptibility.¹ Virologic response rates at 12 weeks were lower in subjects with genotype 1a virus with the NS3 Q80K polymorphism at baseline compared with subjects with the genotype 1a virus without the Q80K polymorphism.¹ Cross-resistance is expected among NS3/4A protease inhibitors. The R155K polymorphism, which emerged frequently in subjects not achieving a sustained virologic response, has been shown to reduce the anti-HCV activity of boceprevir and telaprevir.¹

PHARMACOKINETICS

Simeprevir peak plasma concentrations occurred 4 to 6 hours after oral administration.^{1,5} Plasma concentrations and area under the curve increased more than dose proportionally after multiple doses between 75 and 200 mg, with accumulation occurring after repeated dosing. Steady state was reached after 7 days of once-daily dosing.¹ Administration with a normal calorie breakfast and a high-fat, high-calorie breakfast increased the relative bioavailability by 69% and 61%, respectively, and delayed the absorption by 1 to 1.5 hours.¹

Simeprevir is extensively plasma protein bound (greater than 99.9%), primarily to albumin.¹ The terminal elimination half-life of simeprevir is 10 to 13 hours in HCV-uninfected subjects and 41 hours in HCV-infected subjects receiving a 200 mg dose.¹ Simeprevir is metabolized in the liver, primarily via oxidative metabolism by the hepatic cytochrome P450 3A (CYP3A) system. Elimination is via biliary excretion; renal clearance is insignificant. Unchanged simeprevir in feces accounts for 31% of the administered dose.¹

Simeprevir exposure was increased 2.4-fold in HCV-uninfected subjects with moderate hepatic impairment (Child Pugh class B) and 5.2-fold in HCV-uninfected subjects with severe hepatic impairment (Child Pugh class C). Simeprevir pharmacokinetics have not been assessed in HCV-infected patients with moderate to severe hepatic impairment. Liver fibrosis stage did not have a clinically important effect on simeprevir pharmacokinetics.¹ Simeprevir exposure is increased in Asian patients compared with White patients, with a mean simeprevir plasma exposure 3.4-fold higher.¹ Age, renal function, weight, and gender appear to have no clinically important effect on simeprevir pharmacokinetics.^{1,8}

COMPARATIVE EFFICACY**Indication: Chronic Hepatitis C Virus Genotype 1****Guidelines**

Guideline: An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases

Reference: Ghany MG, et al, 2011⁹

Comments: These guidelines were published prior to the availability of simeprevir; however, the NS3/4A protease inhibitors (boceprevir and telaprevir) are included in the guideline. The optimal therapy recommended by the guideline for chronic HCV genotype 1 infection is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. The NS3/4A protease inhibitors should not be used without peginterferon alfa and weight-based ribavirin.

Studies

Drug: Simeprevir plus Peginterferon Alfa and Ribavirin vs Placebo plus Peginterferon Alfa and Ribavirin

Reference: Manns M, et al, 2011 (OPERA-1; TMC435-C201)¹⁰

Study Design: Phase 2a, randomized, placebo-controlled multicenter study

Study Funding: Tibotec Pharmaceuticals

Patients: The study population consisted of treatment-naïve and treatment-experienced adult patients with chronic HCV genotype 1 infection.

Intervention: The treatment-naïve patients ($n = 74$) were randomly assigned treatment with simeprevir 25, 75, or 200 mg, or placebo once daily for 7 days. After day 7, these patients had peginterferon alfa-2a and ribavirin added to their drug regimen for 21 days. The treatment-experienced patients ($n = 37$; 67% with cirrhosis [Child-Pugh class A], 67.6% were nonresponders, and 32.4% were relapsers) were randomly assigned treatment with simeprevir 75, 150, or 200 mg, or placebo once daily plus peginterferon alfa-2a and ribavirin for 28 days. All patients in both groups were allowed to continue their peginterferon and ribavirin therapy up to week 48.

Results**Primary Endpoint(s)**

- Treatment-naïve patients:
  - Rapid decline in HCV RNA level by day 3; HCV RNA reductions at day 7 were 2.63 $\log_{10}$ units/mL with simeprevir 25 mg, 3.43

$\log_{10}$ units/mL with simeprevir 75 mg, 4.13 $\log_{10}$ units/mL with simeprevir 200 mg, and +0.02 $\log_{10}$ units/mL with placebo.

- HCV RNA reductions at day 28 after the addition of peginterferon and ribavirin to the drug regimen on day 8 were -4.74 $\log_{10}$ units/mL with simeprevir 25 mg, -5.52 $\log_{10}$ units/mL with simeprevir 75 mg, -5.44 $\log_{10}$ units/mL with simeprevir 200 mg, and -3.64 $\log_{10}$ units/mL with placebo.
- Treatment-experienced patients:
  - HCV RNA reductions at day 28 after the addition of peginterferon and ribavirin to the drug regimen on day 8 were -4.28 $\log_{10}$ units/mL with simeprevir 75 mg, -5.46 $\log_{10}$ units/mL with simeprevir 150 mg, -5.26 $\log_{10}$ units/mL with simeprevir 200 mg, and -1.53 $\log_{10}$ units/mL with placebo.
  - Mean reduction in HCV RNA was greater in prior relapsers than previous nonresponders.

Secondary Endpoint(s)

- Treatment-naïve patients:
  - Achievement of an HCV RNA level of less than 25 units/mL at day 28 occurred in all patients treated with the simeprevir-based triple therapy compared with 44% of patients treated with the placebo plus peginterferon and ribavirin regimen.
  - Undetectable HCV RNA levels at day 28 (or rapid virological response) were achieved in 88.9% of the simeprevir 75 mg group, 70% of the simeprevir 200 mg group, and 22.2% of the placebo group.
- Treatment-experienced patients:
  - Achievement of an HCV RNA level of 25 units/mL at day 28 occurred in all prior relapsers and 47% of prior nonresponders treated with the simeprevir-based triple therapy compared with none of the patients taking placebo plus peginterferon and ribavirin regimen.

Comments: Interim results at day 28 were reported; the results from the continuation phase of the study were not available.

Drug: Simeprevir plus Peginterferon and Ribavirin vs Placebo plus Peginterferon and Ribavirin

Reference: Fried MW, et al, 2013 (PILLAR; TMC435-C205)¹¹⁻¹³

Study Design: Randomized, phase 2b, double-blind, placebo-controlled, multicenter study

Study Funding: Tibotec Pharmaceuticals

Patients: 386 treatment-naïve adults with chronic HCV genotype-1 infection and plasma HCV RNA greater than 100,000 units/mL (80% had levels exceeding 800,000 units/mL; 9% to 23% META-VIR stage F3; 10% had NS3 Q80K polymorphism at baseline) included in the intent-to-treat analysis; median age, 46.5 years; 92.5% of patients completed the study.

Intervention: Patients were randomized to 1 of 5 treatment arms:

- Simeprevir 75 mg orally (PO) once daily, peginterferon alfa-2a, and ribavirin for 12 weeks followed by peginterferon and ribavirin for 12 weeks.
- Simeprevir 150 mg PO once daily, peginterferon alfa-2a, and ribavirin for 12 weeks followed by peginterferon and ribavirin for 12 weeks.
- Simeprevir 75 mg PO once daily, peginterferon alfa-2a, and ribavirin for 24 weeks.
- Simeprevir 150 mg PO once daily, peginterferon alfa-2a, and ribavirin for 24 weeks.
- Placebo, peginterferon alfa-2a, and ribavirin for 24 weeks followed by peginterferon and ribavirin for 24 weeks.

The dose of peginterferon alfa-2a was 180 mcg once weekly. The ribavirin dose was 1,000 to 1,200 mg/day. If the HCV RNA was less than 25 units/mL at week 4 and undetectable at weeks 12, 16, and 20, treatment was completed at week 24. All other patients continued peginterferon and ribavirin for up to 48 weeks.

Results**Primary Endpoint(s)**

- Sustained viral response at week 72 (SVR72): 80.8% with simeprevir 75 mg orally once daily, peginterferon, and ribavirin for 12 weeks followed by peginterferon and ribavirin for 12 weeks ($P < .05$ vs control; number needed to treat [NNT], 6.3); 77.9% with simeprevir 150 mg PO once daily, peginterferon, and ribavirin for 12 weeks followed by peginterferon and ribavirin for 12 weeks ($P < .05$ vs control; NNT, 7.7); 70.7% with simeprevir 75 mg PO once daily, peginterferon, and ribavirin for 24 weeks ($P < .05$ vs control; NNT, 17.3); 84.8% with simeprevir 150 mg PO once daily, peginterferon, and ribavirin for 24 weeks ($P < .005$ vs control; NNT, 5.1); 64.9% with placebo, peginterferon, and ribavirin for 24 weeks followed by peginterferon and ribavirin for 24 weeks.

Secondary Endpoint(s)

- A rapid viral response (HCV undetectable at 4 weeks) was achieved in 68% to 76% of the patients treated with a simeprevir-containing regimen, of whom 88% to 95% subsequently achieved SVR24; 5.2% of patients in the placebo arm experienced a rapid viral response.
- SVR12 was achieved in 76% to 86% of the patients treated with a simeprevir-containing regimen compared with 66% treated with control.
- SVR24 was achieved in 75% to 86% of the patients treated with a simeprevir-containing regimen compared with 65% treated with control ($P < .05$ vs control except for the regimen containing simeprevir 75 mg for 24 weeks).
- 79% to 86% of the simeprevir-treated patients were able to complete treatment at week 24.
- Among patients with undetectable HCV RNA at the end of treatment, viral relapse was less frequent in the simeprevir-treated patients (12% vs 18%).
- Fatigue scores over the 72-week study period were lower in the simeprevir-treatment groups ($P < .001$), likely due to the shorter mean treatment duration in these groups; rates of anemia, neutropenia, and rash did not differ between simeprevir and placebo.

Endpoint(s)

- Overall SVR24 rates were lower for patients with HCV genotype 1a (66%) compared with patients with HCV genotype 1b (89%), although SVR24 rates in genotype 1a and 1b patients treated with simeprevir 150 mg were similar (82% and 84%, respectively).
- A predictive value of the IL28B genotype and serum IP-10 response was found in the peginterferon and ribavirin treatment arm, but it had limited predictive value in patients treated with simeprevir, peginterferon, and ribavirin.¹⁴
- PILLAR allowed 53 patients with a Metavir score of F3 (moderate periportal inflammation, piecemeal necrosis or severe focal cell damage, some fibrosis, and no obvious cirrhosis) to be enrolled. The SVR24 in the treatment-naïve F3 patients was 79% with simeprevir, peginterferon, and ribavirin versus 72% with peginterferon and ribavirin.¹⁵ SVR72 rates were 82% and 85% with simeprevir 75 and 150 mg, respectively, and 64% with placebo in patients with Metavir scores of F0 to F2. For patients

with F3 scores, SVR72 rates were 63% and 75% with simeprevir 75 and 150 mg, respectively, and 71% with placebo.¹³

- Among patients with HCV genotype 1a, those without the Q80K polymorphism at baseline experienced a higher SVR24 rate (71% and 86%, respectively with simeprevir 75 and 150 mg) compared with those with the Q80K polymorphism (55% and 67%, respectively, with simeprevir 75 and 150 mg).

Comments: The addition of simeprevir to the peginterferon and ribavirin regimen produced an increased sustained viral release without increasing the incidence of fatigue.¹⁶ Subtle differences between simeprevir 75 and 150 mg doses in response rates in patients with the 1a genotype, non-CC IL28B genotypes, higher body mass index (BMI), and Metavir F3 scores prompted selection of the 150 mg dose for further study. The study was conducted in 13 countries in North America, Europe, and Asia-Pacific regions; 68% of patients were enrolled in Europe, 21% in North America, and 11% in Australia and New Zealand. A similar smaller study (DRAGON) conducted in Japan assessed simeprevir 50 or 100 mg once daily with peginterferon alfa-2a and ribavirin in patients with HCV genotype 1, achieving SVR24 rates of 77% to 92% with simeprevir-containing regimens compared with 46% with placebo plus peginterferon and ribavirin.¹⁷

Limitations: The study excluded patients with cirrhosis.

Drug: Simeprevir plus Peginterferon Alfa-2a and Ribavirin vs Placebo plus Peginterferon Alfa-2a and Ribavirin

Reference: Jacobson J, et al, 2013 (QUEST-1; TMC435-C208)^{1,18,19}

Study Design: Randomized, phase 3, double-blind, multicenter study

Study Funding: Janssen Research

Patients: 394 treatment-naïve patients with chronic HCV genotype-1 infection, compensated liver disease (including cirrhosis), and HCV RNA of at least 10,000 units/mL

Intervention: Patients were randomized 2:1 to treatment with simeprevir 150 mg once daily plus peginterferon alfa-2a and ribavirin or placebo plus peginterferon alfa-2a and ribavirin for 12 weeks. Peginterferon alfa-2a 180 mcg was given as an

injection once each week. Ribavirin was taken as a tablet twice daily at a dose determined by the patient's body weight. Peginterferon alfa-2a and ribavirin were continued in placebo-treated patients for an additional 36 weeks (48 weeks total). The total duration of peginterferon alfa-2a and ribavirin therapy in the simeprevir-treated patients was based on response-guided criteria. If the HCV RNA was less than 25 units/mL at week 4 and undetectable at week 12, therapy was stopped at week 24. Therapy was continued to week 48 for those who did not achieve these criteria.

Results

Primary Endpoint(s)

- SVR12 was 80% in the simeprevir-treated group and 50% in the placebo group ($P < .001$).

Secondary Endpoint(s)

- Rapid viral response was achieved by 80% of the simeprevir-treated group and 12% of the placebo-treated group.
- On-treatment failure rate was 9% in the simeprevir-treated group and 34% in the placebo-treated group.
- Relapse rate was 9% in the simeprevir-treated group and 21% in the placebo-treated group.

Comments: Eighty-five percent of the simeprevir-treated group met the response-guided therapy criteria and had their therapy discontinued at week 24. Presented data were from an analysis conducted at week 60.

Limitations: Data are only available as a meeting abstract and in the prescribing information.

Drug: Simeprevir plus Peginterferon Alfa-2 and Ribavirin vs Placebo plus Peginterferon Alfa-2 and Ribavirin

Reference: Manns M, et al, 2013 (QUEST-2)^{1,19,20}

Study Design: Randomized, phase 3, double-blind, multicenter study

Study Funding: Janssen Research

Patients: 391 treatment-naïve patients with chronic HCV genotype-1 infection, compensated liver disease (including cirrhosis), and HCV RNA of at least 10,000 units/mL.

Intervention: Patients were randomized 2:1 to treatment with simeprevir 150 mg once daily plus peginterferon alfa-2 and ribavirin or placebo plus peginterferon alfa-2 and ribavirin for 12 weeks. Peginterferon alfa-2a 180 mcg was given as an injection once each week and peginterferon alfa-

2b was given as an injection once each week at a dose determined by the patient's body weight. Ribavirin was taken as a tablet twice daily at a dose determined by the patient's body weight. Peginterferon alfa-2 and ribavirin were continued in placebo-treated patients for additional 36 weeks (48 weeks total). The total duration of peginterferon alfa-2 and ribavirin therapy in the simeprevir-treated patients was based on response-guided criteria. If the HCV RNA was less than 25 units/mL at week 4 and undetectable at week 12, therapy was stopped at week 24. Therapy was continued to week 48 for those who did not achieve these criteria.

Results

Primary Endpoint(s)

- SVR12 was 81% in the simeprevir-treated group and 50% in the placebo-treated group ($P < .001$).

Secondary Endpoint(s)

- Rapid viral response was achieved in 79% of the simeprevir-treated group and 13% of the placebo-treated group.
- On-treatment failure rate was 7% in the simeprevir-treated group and 32% in the placebo-treated group.
- Relapse rate was 13% in the simeprevir-treated group and 24% in the placebo-treated group.
- SVR12 in patients treated with peginterferon alfa-2a was 88% in the simeprevir-treated group and 62% in the placebo-treated group.
- SVR12 in patients treated with peginterferon alfa-2b was 78% in the simeprevir-treated group and 42% in the placebo-treated group.
- SVR12 for patients with a Metavir score of F0 to F2 was 85% in the simeprevir-treated group and 51% in the placebo-treated group.
- SVR12 for patients with a Metavir score of F3 to F4 was 66% in the simeprevir-treated group and 47% in the placebo-treated group.

Comments: Study allowed the use of peginterferon alfa-2a and peginterferon alfa-2b. In the simeprevir-treated group, 86% met the response-guided therapy criteria and had their therapy discontinued at week 24. Presented data were from an analysis conducted at week 60. In pooled data from this study and the QUEST 1 study, SVR12 rates were lower in patients with the Q80K polymorphism at baseline than those without the Q80K polymorphism. Among patients with HCV genotype 1a, SVR12

was achieved in 84% of simeprevir-treated patients without the polymorphism compared with 43% of placebo-treated patients without the polymorphism, and in 58% of simeprevir-treated patients with the polymorphism compared with 52% of placebo-treated patients with the polymorphism.¹

Limitations: Data are only available as a meeting abstract and in the prescribing information.

Drug: Simeprevir plus Peginterferon Alfa-2a and Ribavirin vs Placebo plus Peginterferon Alfa-2a and Ribavirin

Reference: *Olysio* package insert, 2013 (PROMISE)¹

Study Design: Randomized, phase 3, double-blind, multicenter study

Study Funding: Janssen Research

Patients: 393 patients with chronic HCV genotype-1 infection, compensated liver disease (including cirrhosis), and HCV RNA of at least 10,000 units/mL (84% had HCV RNA greater than 800,000 units/mL; 15% had Metavir score F3 and 15% had Metavir score F4; 42% had HCV genotype 1a and 58% had HCV genotype 1b; 13% overall and 31% with genotype 1a virus had the NS3 Q80K polymorphism at baseline), who had relapsed after therapy with peginterferon and ribavirin; median age was 52 years; 66% of patients were male and 94% were White.

Intervention: Simeprevir 150 mg once daily plus peginterferon alfa-2 and ribavirin or placebo plus peginterferon alfa-2 and ribavirin for 12 weeks. Peginterferon alfa-2a 180 mcg was given as an injection once each week. Ribavirin was taken as a tablet twice daily at a dose determined by the patient's body weight. Peginterferon alfa-2a and ribavirin were continued in placebo-treated patients for an additional 36 weeks (48 weeks total). The total duration of peginterferon alfa-2 and ribavirin therapy in the simeprevir-treated patients was based on response-guided criteria. If the HCV RNA was less than 25 units/mL at week 4 and undetectable at week 12, therapy was stopped at week 24. Therapy was continued to week 48 for those who did not achieve these criteria.

Results

Primary Endpoint(s)

- SVR12 was 79% in the simeprevir-treated group and 37% in the placebo-treated group.

Secondary Endpoint(s)

- Rapid viral response was achieved in 77% of the simeprevir-treated group.
- On-treatment failure rate was 3% in the simeprevir-treated group and 27% in the placebo-treated group.
- Relapse rate was 18% in the simeprevir-treated group and 48% in the placebo-treated group.
- SVR12 for patients with genotype 1a virus was 70% in the simeprevir-treated group and 28% in the placebo-treated group. Among those without the Q80K polymorphism, SVR12 was achieved in 78% in the simeprevir group and 26% in the placebo group. Among those with the Q80K polymorphism, SVR12 was achieved in 47% in the simeprevir group and 30% in the placebo group.
- SVR12 for patients with genotype 1b virus was achieved in 86% with simeprevir treatment compared with 43% in the placebo group.
- SVR12 for patients with a Metavir score of F0 to F2 was 82% in the simeprevir-treated group and 41% in the placebo-treated group.
- SVR12 for patients with a Metavir score of F3 to F4 was 73% in the simeprevir-treated group and 24% in the placebo-treated group.

Comments: Response rates were higher in the simeprevir-treated patients compared with the placebo treatment group when assessed by gender, age, race, BMI, HCV genotype/subtype, baseline HCV RNA load, prior HCV therapy, Metavir fibrosis score, and IL28B genotype.

Limitations: Data are only available in the prescribing information.

Drug: Simeprevir plus Peginterferon and Ribavirin vs Placebo plus Peginterferon and Ribavirin

Reference: Zeuzem S, et al, 2011; Poordad F, et al, 2012; Zeuzem S, et al, 2012 (ASPIRE)²¹⁻²⁴

Study Design: Randomized, phase 2b, double-blind, placebo-controlled, multicenter study

Study Funding: Tibotec Pharmaceuticals

Patients: 462 treatment-experienced adults with chronic HCV genotype-1 infection and HCV RNA greater than 10,000 units/mL (86% had HCV RNA greater than 800,000 units/mL; 58% with genotype 1b; 19% with F3 METAVIR score and 18% with F4 score; 12% with NS3 Q80K polymorphism at baseline) were included in the intent-to-treat analysis; median age was 50 years, 67% of patients were male and 93% were White. Patients had to

have been treated with at least 1 previous course of peginterferon and ribavirin and were classified as null responders (less than 2 log₁₀ reduction in HCV RNA by week 12; 25% of patients), partial responders (at least 2 log₁₀ reduction in HCV RNA by week 12; detectable HCV RNA at end of treatment; 35% of patients), or relapsers (HCV RNA undetectable at end of treatment; detectable within 24 weeks posttreatment; 40% of patients); 91.6% of patients completed the study.

Intervention: Patients were randomized to 1 of 7 treatment arms:

- Simeprevir 100 mg PO once daily, peginterferon, and ribavirin for 12 weeks followed by placebo plus peginterferon and ribavirin for 36 weeks.
- Simeprevir 150 mg PO once daily, peginterferon, and ribavirin for 12 weeks followed by placebo plus peginterferon and ribavirin for 36 weeks.
- Simeprevir 100 mg PO once daily, peginterferon, and ribavirin for 24 weeks followed by placebo plus peginterferon and ribavirin for 24 weeks.
- Simeprevir 150 mg PO once daily, peginterferon, and ribavirin for 24 weeks followed by placebo plus peginterferon plus ribavirin for 24 weeks.
- Simeprevir 100 mg PO once daily, peginterferon, and ribavirin for 48 weeks.
- Simeprevir 150 mg PO once daily, peginterferon, and ribavirin for 48 weeks.
- Placebo plus peginterferon and ribavirin for 48 weeks

Peginterferon was administered at a dose of 180 mcg subcutaneously once weekly. Ribavirin was administered orally at a dose of 1,000 or 1,200 mg/day. All study medication was discontinued in patients not achieving at least a 1 log₁₀ reduction in HCV RNA at week 4, a 2 log₁₀ reduction at week 12, or HCV RNA less than 25 units/mL at weeks 24 or 36; study medication was also discontinued in patients with viral breakthrough.

Results**Primary Endpoint(s)**

- SVR24: 70% with simeprevir 100 mg PO once daily, peginterferon, and ribavirin for 12 weeks followed by placebo and peginterferon plus ribavirin for 36 weeks ($P < .001$ vs control; NNT, 2.2); 67% with simeprevir 150 mg PO once daily, peginterferon, and ribavirin

for 12 weeks followed by placebo and peginterferon plus ribavirin for 36 weeks ($P < .001$ vs control; NNT, 2.3); 66% with simeprevir 100 mg PO once daily, peginterferon, and ribavirin for 24 weeks followed by placebo and peginterferon plus ribavirin for 24 weeks ($P < .001$ vs control; NNT, 2.4); 72% with simeprevir 150 mg PO once daily, peginterferon, and ribavirin for 24 weeks followed by placebo and peginterferon plus ribavirin for 24 weeks ($P < .001$ vs control; NNT, 2.1); 61% with simeprevir 100 mg PO once daily, peginterferon, and ribavirin for 48 weeks ($P < .001$ vs control; NNT, 2.7); 80% with simeprevir 150 mg PO once daily, peginterferon, and ribavirin for 48 weeks ($P < .001$ vs control; NNT, 1.8); 23% with placebo, peginterferon, and ribavirin for 48 weeks.

Secondary Endpoint(s)

- Rapid viral response (HCV RNA undetectable at week 4) was achieved in 53% to 68% of patients receiving a simeprevir-containing regimen compared with 1.5% receiving placebo; among patients achieving a rapid viral response, 90% and 86% in the simeprevir 100 and 150 mg groups, respectively, achieved SVR24.
- SVR12 was achieved in 61% to 80% of simeprevir-treated patients compared with 23% treated with placebo.
- Neutropenia, rash, and pruritus occurred more frequently during simeprevir treatment; fatigue scores did not differ between treatment groups.

Endpoint(s)

- **Table 2** summarizes the SVR24 results by previous treatment response (prior null responder, prior partial responder, or prior relapser).
- The main reasons for failure to achieve SVR in the simeprevir-treated patients were viral breakthrough (10.9%) and relapse (11.9%), and the majority of these patients (92.6%) had emerging mutations with reduced in vitro susceptibility to simeprevir.²⁵
- ASPIRE allowed patients with a Metavir score of F3/F4 (moderate periportal inflammation, piecemeal necrosis or severe focal cell damage, some fibrosis, and no obvious cirrhosis to severe periportal inflammation, piecemeal necrosis or bridging necrosis, and cirrhosis) to be enrolled. The SVR24 in the treatment-experienced F3 patients was 48% with simeprevir, peginterferon, and ribavirin versus 8% with placebo

plus peginterferon and ribavirin. The SVR24 in the treatment-experienced F4 patients was 62% with simeprevir, peginterferon, and ribavirin versus 0% with placebo plus peginterferon and ribavirin.¹⁵

- In prior null responders, SVR24 rates with simeprevir 150 mg were 42% for genotype 1a and 58% for genotype 1b, compared with 0% and 33%, respectively, with placebo. Simeprevir response rates did not differ between patients with the Q80K polymorphism and those without the polymorphism.

Comments: Higher responses occurred with all drug regimens containing simeprevir and were generally similar or higher when the dose of simeprevir was 150 mg.^{22,23} The study was conducted in 14 countries in Europe, North America, Australia, and New Zealand; the percentage of patients enrolled in each region was not provided.

Limitations: This is a phase 2 study assessing multiple doses and regimens; results of a phase 3 study in treatment-experienced patients are not yet available.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Contraindications for simeprevir are similar to those found in the boceprevir and telaprevir labeling (see **Table 3**).

Warnings and Precautions

Simeprevir must not be used as monotherapy. It should be used in conjunction with peginterferon alfa and ribavirin, and the contraindications, warnings, and precautions associated with those therapies must be heeded. The warnings and precautions for simeprevir, boceprevir, and telaprevir are compared in **Table 4**.

Photosensitivity reactions have been observed during therapy with simeprevir plus peginterferon alfa and ribavirin, including serious reactions resulting in hospitalization. Photosensitivity reactions occurred most frequently within the first 4 weeks of combined therapy with simeprevir, peginterferon alfa, and ribavirin, but can occur at any time during treatment. It may present as an exaggerated sunburn reaction, usually affecting areas exposed to light, and manifest with burning, erythema, exudation, blistering, and edema. Discontinuation of therapy may be necessary for some patients.¹

Table 2. SVR24 in treatment-experienced adults with chronic HCV genotype-1 infection: Interim results from the ASPIRE Trial²³

	Prior null responder	Prior partial responder	Prior relapser
Simeprevir 100 mg 12 wk + peginterferon/ribavirin 48 wk (<i>n</i> = 66)	38%	70%	89%
Simeprevir 150 mg 12 wk + peginterferon/ribavirin 48 wk (<i>n</i> = 66)	53%	65%	77%
Simeprevir 100 mg 24 wk + peginterferon/ribavirin 48 wk (<i>n</i> = 65)	56%	48%	89%
Simeprevir 150 mg 24 wk + peginterferon/ribavirin 48 wk (<i>n</i> = 68)	41%	75%	89%
Simeprevir 100 mg 48 wk + peginterferon/ribavirin 48 wk (<i>n</i> = 66)	44%	55%	77%
Simeprevir 150 mg 48 wk + peginterferon/ribavirin 48 wk (<i>n</i> = 65)	59%	86%	89%
Placebo + peginterferon/ribavirin 48 wk (<i>n</i> = 66)	19%	9%	37%

Note: SVR24 = sustained viral response at week 24.

Table 3. Comparison of the contraindications for simeprevir, boceprevir, sofosbuvir, and telaprevir¹⁻⁴

	Simeprevir	Boceprevir	Sofosbuvir	Telaprevir
Contraindications to peginterferon alfa ^a	X	X	X	X
Contraindications to ribavirin ^a	X	X	X	X
CYP3A substrates		X		X
Potent CYP3A inducers	X ^b	X		X
Pregnancy ^c	X	X	X	X
History of hypersensitivity to drug		X		

^aMust be used in combination with these drugs; except sofosbuvir, which might be used with ribavirin without the peginterferon for certain HCV infections.

^bNot contraindicated, but use with moderate or strong CYP3A inducers or inhibitors is not recommended.

^cContraindicated because of the required peginterferon and/or ribavirin therapy.

Rash has also been observed in patients treated with a regimen of simeprevir, peginterferon, and ribavirin. It has occurred most frequently in the first 4 weeks of therapy, but can occur at any time during treatment. Although most events have been of mild to moderate severity, severe rash and rash requiring discontinuation of therapy have been reported. Patients with mild to moderate rash should be followed for possible rash progression, with discontinuation of therapy advised if the rash becomes severe.¹

Simeprevir contains a sulfonamide moiety. Although an increased incidence of rash or photosensitivity were not observed in the small number of patients with a history of sulfa allergy exposed to simeprevir in clinical trials (*n* = 16), the risk of adverse reactions associated with sulfa allergy cannot be excluded.¹

Higher simeprevir exposure has also been observed in patients of East Asian ancestry, potentially increasing the frequency of adverse reactions including rash and photosensitivity.¹

The safety and efficacy of simeprevir have not been studied in patients with moderate or severe hepatic impairment (Child Pugh class B or C). Simeprevir exposure may be increased, resulting in an increased frequency of adverse reactions including rash and photosensitivity. No specific recommendations for dosage adjustment are available.¹

No simeprevir dose adjustment is required in patients with mild, moderate, or severe renal impairment.¹

Because of the embryo-fetal toxicity associated with the required ribavirin therapy, female patients of childbearing potential and their male partners, as

Table 4. Comparison of the warnings and precautions for simeprevir, boceprevir, sofosbuvir, and telaprevir¹⁻⁴

	Simeprevir	Boceprevir	Sofosbuvir	Telaprevir
All cautions associated with peginterferon alfa	X	X	X ^a	X
All cautions associated with ribavirin	X	X	X	X
Reduced hemoglobin concentrations		X		X
Anemia		X		X
Neutropenia		X		
Fatal and nonfatal serious skin reactions				X ^b
Skin rashes	X			X
Photosensitivity	X			
Sulfa allergy	X			
Hypersensitivity		X		
Drug interactions: CYP3A	X	X		X
Drug interactions: Potent P-glycoprotein inducers			X	
Pregnancy	Category C	Category B	Category B	Category B
Pregnancy category of therapy; because of the required concurrent peginterferon and/or ribavirin therapy	Category X	Category X	Category X	Category X

^aOnly if the peginterferon is part of the drug regimen.^bBoxed warning.

well as male patients and their female partners, must use 2 effective contraceptive methods during treatment and for at least 6 months after completion of treatment. Routine monthly pregnancy tests must be performed during this time.¹

Breast-feeding should be done with caution. It is not known if simeprevir or its metabolites are excreted in human breast milk. It can be detected in a suckling rat, indicating the drug is excreted in milk. A decision should be made regarding breast-feeding based on the potential risk to the infant and the importance of therapy to the mother; the manufacturer recommends that either the drug or breast-feeding should be discontinued.¹

ADVERSE REACTIONS

Adverse reactions occurring with at least 3% higher frequency in subjects treated with simeprevir 150 mg once daily in combination with peginterferon alfa and ribavirin than in subjects treated with placebo with peginterferon alfa and ribavirin are summarized in **Table 5**.¹ The most frequently reported adverse reactions associated with simeprevir-containing regimens included fatigue, headache, pruritus, influenza-like illness, rash, neutropenia, and nausea.^{10,11,18,20,26} The incidence of adverse reactions might be slightly higher with simeprevir, peginter-

feron, and ribavirin compared with peginterferon and ribavirin alone with no increase in severity.²⁶ The addition of simeprevir to a peginterferon and ribavirin regimen did not change the incidence of patient-reported fatigue.¹⁶

There were no differences between treatment groups in hemoglobin, neutrophils, platelets, AST, ALT, amylase, or serum creatinine. Increased alkaline phosphatase and hyperbilirubinemia were observed more frequently in simeprevir-treated patients than in placebo-treated patients. Elevations in bilirubin were generally mild to moderate, peaked within the first 2 weeks of therapy, and were rapidly reversible upon cessation of simeprevir.¹ Increases in total (direct and indirect) bilirubin without concomitant changes in ALT or AST have been potentially attributed to a reversible inhibition of OATP1B1 and MRP2 transporters.²⁶

DRUG INTERACTIONS

Coadministration of simeprevir with moderate or strong inducers or inhibitors of CYP3A is not recommended because such combinations may lead to lower or higher simeprevir exposure.¹ Simeprevir does not affect CYP2C9, CYP2C19, or CYP2D6. It does mildly inhibit CYP1A2 and CYP3A4 activity, but does not inhibit hepatic CYP3A4 activity. Coad-

Table 5. Adverse reaction occurring more frequently with simeprevir plus peginterferon alfa and ribavirin than with placebo plus peginterferon alfa and ribavirin¹

	Simeprevir + peginterferon alfa + ribavirin (n = 781)	Placebo + peginterferon alfa + ribavirin (n = 397)
Rash (including photosensitivity)	28%	20%
Pruritus	22%	15%
Nausea	22%	18%
Myalgia	16%	13%
Dyspnea	12%	8%

ministration with CYP3A4 substrates may result in increased concentrations of these drugs. Simeprevir also inhibits OATP1B1/3 and P-glycoprotein transporters, potentially resulting in increased plasma concentrations of drugs that are substrates for these transporters.¹ **Table 6** lists the established or potentially significant drug interactions associated with simeprevir.¹ No dose adjustments are needed for either drug when simeprevir is administered with caffeine, dextromethorphan, escitalopram, ethinyl estradiol plus norethindrone, methadone, midazolam (intravenous), omeprazole, raltegravir, rilpivirine, and tenofovir disoproxil fumarate.²⁷⁻²⁹ In addition, no clinically important interactions are anticipated when simeprevir is administered with antacids; the corticosteroids budesonide, fluticasone, methylprednisolone, and prednisone; fluvastatin; H₂-receptor antagonists; the narcotic analgesics buprenorphine and naloxone; the nucleoside reverse transcriptase inhibitors abacavir, didanosine, emtricitabine, lamivudine, stavudine, and zidovudine; maraviroc; methyphenidate; and proton pump inhibitors.¹

RECOMMENDED MONITORING

The monitoring requirements for simeprevir are less than those recommended with boceprevir and telaprevir therapy (see **Table 7**). Hematologic monitoring is recommended at baseline and at weeks 2 and 4 of ribavirin therapy, and then as clinically appropriate.³⁰

DOSING

The recommended dose of simeprevir is 150 mg once daily with food. In all patients, simeprevir therapy should be initiated in combination with peginterferon alfa and ribavirin and continued for 12 weeks. Treatment-naïve patients and prior relapsers, including those with cirrhosis, should receive an additional 12 weeks of therapy with peginterferon alfa and ribavirin (total treatment duration, 24 weeks). Prior

nonresponders (partial and null responders), including those with cirrhosis, should receive an additional 36 weeks of peginterferon and ribavirin (total treatment duration, 48 weeks).¹ Patients failing to achieve a virologic response while on therapy are unlikely to achieve a sustained virologic response; therefore, therapy should be discontinued in patients with an HCV RNA of 25 units/mL or greater at weeks 4, 12, or 24.¹

Boceprevir is dosed as four 200 mg capsules 3 times daily with food, starting after 4 weeks of peginterferon and ribavirin therapy continuing for up to 44 weeks.² Sofosbuvir is dosed as 400 mg once daily with or without food for 12 weeks in patients with genotype 1 (with peginterferon and ribavirin), 2 (with ribavirin), or 4 (with peginterferon and ribavirin), and 24 weeks in genotype 3 (with ribavirin).⁴ Telaprevir is dosed as three 375 mg tablets twice daily with food (meal or snack containing at least 20 g of fat) for 12 weeks with peginterferon and ribavirin; peginterferon and ribavirin therapy follows for an additional 12 or 36 weeks, depending on viral response and prior response status.³

PRODUCT AVAILABILITY

Simeprevir received FDA approval on November 22, 2013.³¹ It is available as 150 mg capsules supplied in bottles of 7 or 28 capsules. Simeprevir capsules should be stored in the original bottle to protect the product from light and at temperatures below 30°C (86°F).¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS was required for simeprevir approval.³¹

CONCLUSION

Simeprevir is an HCV NS3/4A protease inhibitor that will be useful in combination with peginterferon alfa and ribavirin in the treatment of chronic HCV genotype 1 in adult patients with compensated

Table 6. Simeprevir drug interactions¹

Class	Drug	Effect	Clinical recommendation
Antiarrhythmics	Digoxin	↑ Digoxin	Monitor digoxin concentrations
	Amiodarone, disopyramide, flecainide, mexiletine, propafenone, quinidine	↑ Antiarrhythmics	Caution, therapeutic drug monitoring if available
Anticoagulants	Warfarin	↔ Warfarin	Monitor international normalized ratio
Anticonvulsants	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	↓ Simeprevir	Avoid concomitant use
Anti-infectives	Erythromycin	↑ Simeprevir, ↑ erythromycin	Avoid concomitant use
	Clarithromycin, telithromycin	↑ Simeprevir	Avoid concomitant use
	Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole	↑ Simeprevir	Avoid concomitant use
	Rifampin, rifabutin, rifapentine	↓ Simeprevir, ↔ antimycobacteria	Avoid concomitant use
Calcium channel blockers	Amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil	↑ Calcium channel blocker	Caution, clinical monitoring
Corticosteroids	Dexamethasone	↓ Simeprevir	Avoid concomitant use
Herbal products	Milk thistle	↑ Simeprevir	Avoid concomitant use
	St. John's wort	↓ Simeprevir	Avoid concomitant use
HIV products	Cobicistat-containing product	↑ Simeprevir	Avoid concomitant use
	Efavirenz	↓ Simeprevir, ↔ efavirenz	Avoid concomitant use
	Delavirdine, etravirine, nevirapine	↑ or ↓ Simeprevir	Avoid concomitant use
	Darunavir/ritonavir	↑ Simeprevir, ↑ darunavir	Avoid concomitant use
	Ritonavir	↑ Simeprevir	Avoid concomitant use
	Atazanavir, fosamprenavir, lopinavir, indinavir, nelfinavir, saquinavir, tipranavir	↑ or ↓ Simeprevir	Avoid concomitant use
HMG Co-A reductase inhibitors	Atorvastatin	↑ Atorvastatin	Use lowest necessary atorvastatin dose, not to exceed 40 mg daily
	Lovastatin, pitavastatin, pravastatin, simvastatin	↑ HMG Co-A reductase inhibitor	Use lowest necessary dose, titrate dose carefully
	Rosuvastatin	↑ Rosuvastatin	Initiate rosuvastatin with 5 mg daily, do not exceed 10 mg daily
Immunosuppressants	Cyclosporine	↑ Cyclosporine	Monitor cyclosporine concentrations
	Sirolimus	↑ or ↓ Sirolimus	Monitor sirolimus concentrations
	Tacrolimus	↓ Tacrolimus	Monitor tacrolimus concentrations

(continued)

Table 6. Simeprevir drug interactions¹ (CONT.)

Class	Drug	Effect	Clinical recommendation
Phosphodiesterase type-5 (PDE-5) inhibitors	Sildenafil, tadalafil, vardenafil	↑ PDE-5 inhibitor	No dose adjustment when used for erectile dysfunction, but reduced doses may be required with long-term use in pulmonary arterial hypertension; start with lowest dose and monitor clinically
Sedatives/Anxiolytics	Midazolam (oral)	↑ Midazolam	Use with caution
	Triazolam (oral)	↑ Triazolam	Use with caution

Table 7. Comparison of the recommended monitoring during HCV antiviral therapy¹⁻⁴

	Simeprevir	Boceprevir	Sofosbuvir	Telaprevir
HCV RNA levels	Weeks 4, 12, and 24	Weeks 4, 8, 12, and 24, and at the end of treatment	X	Weeks 4 and 12
Hemoglobin	^a	Baseline; weeks 2, 4, 8, and 12, and as clinically necessary	^a	Baseline; weeks 2, 4, 8, and 12, and as clinically necessary
Complete blood count	^a	Baseline; weeks 2, 4, 8, and 12, and as clinically necessary	^a	Baseline; weeks 2, 4, 8, and 12, and as clinically necessary
Chemistry (electrolytes, serum creatinine, uric acid, hepatic enzymes, bilirubin, and thyroid-stimulating hormone)	^a	^a	^a	Baseline; weeks 2, 4, 8, and 12, and as clinically necessary

Note: HCV = hepatitis C virus.

^aAs required for ribavirin therapy.

liver disease. Like boceprevir, telaprevir, and sofosbuvir, simeprevir must be used in combination with peginterferon alfa and ribavirin in the treatment of HCV genotype 1 disease. Compared with boceprevir and telaprevir, it offers the advantage of once-daily dosing for 12 weeks, and a slightly different adverse event and drug interaction profile. There are no head-to-head trials with the other NS3/4A protease inhibitors.

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