

Therapeutic Class Overview Hepatitis C Protease Inhibitors

Therapeutic Class

- Overview/Summary:** Included in this review are the hepatitis C protease inhibitors boceprevir (Victrelis[®]), simeprevir (Olysio[®]), and telaprevir (Incivek[®]). All agents are Food and Drug Administration (FDA) approved for the treatment of adults with chronic hepatitis C genotype 1 infection, when used in combination with peg interferon alfa and ribavirin. The hepatitis C protease inhibitors can be used in both treatment naïve and experienced patients, and the specific FDA approved indications are outlined in Table 1.¹⁻³ These direct acting antivirals inhibit the replication of hepatitis C virus (HCV) host cells by binding to the NS3/4A protease of HCV genotype 1a and 1b.¹⁻⁴ Because these agents must be used in combination with peg interferon alfa and ribavirin, the contraindications and warnings associated with those agents are also applicable to the hepatitis C protease inhibitors. In addition, the incidence of rash is increased when the hepatitis C protease inhibitors are used in combination with peg interferon alfa and ribavirin. In contrast to boceprevir or telaprevir combination therapy, simeprevir combination therapy was not associated with additional anemia compared to the standard of care. The frequencies of administration of boceprevir, telaprevir, simeprevir are once daily, two times daily, and three times daily, respectively.¹⁻³ According to the American Association for the Study of Liver Diseases, boceprevir or telaprevir in combination with peg interferon alfa and ribavirin are recommended for the treatment of HCV genotype 1.⁵ Treatment guidelines were published prior to the availability of simeprevir and do not address its place in therapy. No one peg interferon or ribavirin product is preferred or recommended over another.⁵⁻¹⁰ Furthermore, no one hepatitis C protease inhibitor is preferred over another and current recommendations for their use are in line with FDA approved indications and dosing.¹⁻¹⁰ Clinical trials have demonstrated that when a hepatitis C protease inhibitor is added to the current standard of care, sustained virologic response rates are significantly increased.¹¹⁻²³

Table 1. Current Medications Available in Therapeutic Class¹⁻³

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Boceprevir (Victrelis [®])	Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers	Capsule: 200 mg	-
Simeprevir (Olysio [®])	Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers	Capsule: 150 mg	-
Telaprevir (Incivek [®])	Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers	Tablet: 375 mg	-

Evidence-based Medicine

In clinical trials, the addition of hepatitis C protease inhibitors to standard therapy (i.e., peg interferon alfa and ribavirin) resulted in significantly higher sustained virologic response rates compared to standard

therapy alone in adults with chronic hepatitis C genotype 1 infection. These results were achieved in both treatment-naïve and experienced patients. Additionally, results demonstrated that in select patients who achieve an early virologic response with boceprevir or telaprevir-containing regimen, there is potential to decrease the total duration of treatment (24 [telaprevir], 28 [boceprevir] or 36 [boceprevir] vs 48 weeks [standard therapy]). The treatment duration with simeprevir combination therapy is fixed at either 24 or 48 weeks depending on the response to prior treatment with peg interferon alfa and ribavirin. Use of hepatitis C protease inhibitors was also associated with a greater incidence of adverse events, including rash, compared to the standard therapy alone. In contrast to boceprevir or telaprevir combination therapy, simeprevir combination therapy was not associated with additional anemia compared to the standard of care.^{1-3,11-23}

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - The most efficacious therapy for the treatment of hepatitis C virus (HCV) genotype 1 is the use of boceprevir or telaprevir in combination with peg interferon alfa and ribavirin.^{5,6}
 - No one protease inhibitor is preferred or recommended over another.⁵⁻¹⁰
 - No one peg interferon or ribavirin product is preferred or recommended over another.⁵⁻¹⁰
 - Patients with genotype 2 or 3 infection may receive treatment for up to 24 weeks and patients with genotype 1 or 4 infection may receive treatment for up to 48 weeks.⁵⁻¹⁰
 - Treatment guidelines were published prior to the availability of simeprevir and do not address its place in therapy.⁵⁻¹⁰
- Other Key Facts:
 - Boceprevir is available as a 200 mg capsule and is dosed 800 mg three times daily.¹
 - Boceprevir is initiated after a four week lead-in period of peg interferon alfa and ribavirin alone.¹
 - Telaprevir is available as a 375 mg tablet and is dosed 1,125 mg twice daily.²
 - Telaprevir is initiated with peg interferon alfa and ribavirin.²
 - Simeprevir is available as a 150 mg capsule and is dosed 150 mg once daily.³
 - Simeprevir is initiated with peg interferon alfa and ribavirin.³
 - Prior to initiating therapy with simeprevir, patients with HCV genotype 1a should be screened for the presence of NS3 Q80K polymorphism that is associated with substantially reduced drug efficacy; alternative therapy should be considered if this polymorphism is present.³
 - When added to standard therapy, both boceprevir and telaprevir are associated with an increase in the incidence of anemia. In addition, telaprevir is associated with an increase in incidence in rash, which can be serious in nature.^{1,2}
 - Select patients with a satisfactory early virologic response to a regimen containing boceprevir or telaprevir may be candidates for shorter duration of total treatment.^{1,2}
 - If a patient has an undetectable HCV ribonucleic acid (RNA) level at treatment weeks eight and 24 with a boceprevir-containing regimen, 28 or 36 weeks of total treatment is effective in achieving a sustained virologic response (SVR).
 - If a patient has an undetectable HCV RNA level at treatment weeks four and 12 with a telaprevir-containing regimen, 24 weeks of total treatment is effective in achieving an SVR.
 - Futility rules, based on HCV RNA levels, apply to any triple therapy regimen used for the treatment of chronic hepatitis C genotype 1 infection.¹⁻³
 - Futility should be assessed at treatment weeks 12 and 24 with boceprevir-containing regimens, and at treatment weeks four, 12 and 24 with simeprevir and telaprevir-containing regimens.

References

1. Victrelis[®] [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2013 Sep.
2. Incivek[®] [package insert]. Cambridge (MA): Vertex Pharmaceuticals Incorporated; 2013 Oct.
3. Olysio[®] [package insert]. Titusville (NJ): Janssen Therapeutics; 2013 Nov.
4. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Healthcare; Updated periodically [cited 2013 Dec 25]. Available from: <http://www.thomsonhc.com/>.

5. American Association for the Study of Liver Diseases (AASLD). 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 [guideline on the internet]. Geneva, Switzerland: American Association for the Study of Liver Diseases; 2013 [cited 2014 Jan 17]. Available from: <http://www.aasld.org/practiceguidelines/Documents/AASLDUpdateTreatmentGenotype1HCV11113.pdf>.
6. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol*. 2013 Dec 4.
7. Yee HS, Chang MF, Pocha C, Lim J, Ross D, Morgan TR, et al. Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. *Am J Gastroenterol*. 2012 May;107(5):669-89.
8. Dienstag JL, McHutchison JG. American Gastroenterological Association Medical position statement on the management of hepatitis C. *Gastroenterology*. 2006;130(1):225-30.
9. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, Management and treatment of hepatitis C; An Update. 2009. *Hepatology* 2009; 49(4):1-40.
10. Centers for Disease Control and Prevention. The ABCs of Hepatitis Fact Sheet [guideline on the Internet]. Atlanta (GA): CDC 2012 Aug [cited 2014 Jan 16]. Available at: <http://www.cdc.gov/hepatitis/resources/professionals/pdfs/abctable.pdf>.
11. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011 Mar 31;364:1195-206.
12. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011;364:2405-16.
13. Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med*. 2011;365:1014-24.
14. Kumada H, Toyota J, Okanou T, Chayama K, Tsubouchi H, Hayashi N. Telaprevir with peg interferon and ribavirin for treatment-naïve patients chronically infected with HCV of genotype 1 in Japan. *J Hepatol*. 2012 Jan;56(1):78-84.
15. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011 Mar 31;364:1207-17.
16. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med*. 2011;364:2417-28.
17. Hayashi N, Okanou T, Tsubouchi H, Toyota J, Chayama K, Kumada H. Efficacy and safety of telaprevir, a new protease inhibitor, for difficult-to-treat patients with genotype 1 chronic hepatitis C. *J Viral Hepat*. 2012 Feb;19(2):e134-42.
18. Flamm SL, Lawitz E, Jacobson I, Bourlière M, Hezode C, Vierling JM, et al. Boceprevir with peg interferon alfa-2a-ribavirin is effective for previously treated chronic hepatitis C genotype 1 infection. *Clin Gastroenterol Hepatol*. 2013 Jan;11(1):81-87.
19. Kwo PY, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peg interferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomized, multicenter phase 2 trial. *Lancet*. 2010;376:705-16.
20. Jacobson I, Dore GJ, Foster GR, Fried M, Radu M, Rafalskiy V, et al. Simeprevir (TMC435) with peg interferon/ribavirin for chronic HCV genotype-1 infection in treatment-naïve patients: results from QUEST-1, a phase III trial. Poster presented at Digestive Disease Week (DDW); Orlando, FL; May 18-21, 2013. Poster 1674582.
21. Poordad F, Manns M, Marcellin P, Affonso de Araujo ES, Buti M, et al. Simeprevir with peg interferon- α 2a or - α 2b and ribavirin in treatment-naïve HCV genotype-1 patients: QUEST-2, a randomized phase III trial. Data presented at Digestive Disease Week (DDW); Orlando, FL; May 18-21, 2013.
22. Lawitz E, Forns X, Zeuzem S, Gane E, Bronowicki JP, Andreone P et al. Simeprevir with peg interferon/ribavirin for treatment of chronic HCV genotype 1 infection in patients who relapsed after previous interferon-based therapy: results from PROMISE, a phase III trial. Data presented at Digestive Disease Week (DDW); Orlando, FL; May 18-21, 2013.
23. Zeuzem S, Berg T, Gane E, Ferenci P, Foster GR, Fried MW, et al. Simeprevir Increases Rate of Sustained Virologic Response Among Treatment-Experienced Patients with HCV Genotype-1 Infection: a Phase IIb Trial [published online ahead of print]. *Gastroenterology*. 2013 Oct 31.

Therapeutic Class Review Hepatitis C Protease Inhibitors

Overview/Summary

The hepatitis C virus (HCV) is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood. It causes chronic infection in 70 to 85% of infected persons and the Centers for Disease Control and Prevention estimates 3.2 million persons are chronically infected. Chronic HCV infection can lead to the development of active liver disease, and accounts for up to 40% of all patients undergoing liver transplantation.^{1,2} There are seven genotypes of HCV (genotypes 1 to 7), with genotype 1 being the most common in the United States, followed by genotypes 2 and 3.^{2,3} Genotyping is helpful in the clinical management of patients with hepatitis C for predicting the likelihood of response to treatment and in determining the optimal duration of treatment. Treatment goals for the management of chronic hepatitis C include preventing complications and death. Due to the slow evolution of chronic infection, it is difficult to demonstrate if treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virological parameters. Of most importance is sustained virologic response (SVR), which is defined as the absence of HCV ribonucleic acid 24 weeks following discontinuation of treatment.² Of note, SVR rates are lowest with genotype 1 as compared to the other identified genotypes.³ Combination treatment with peg interferon alfa and ribavirin has been the standard of care for the treatment of chronic hepatitis C.²⁻⁶ Newer treatment strategies which aim to improve efficacy, ease of administration, tolerability and patient adherence, as well as to shorten treatment duration are currently being developed and include the newly approved nonstructural protein 3 protease inhibitors, boceprevir, telaprevir, and simeprevir as well as nonstructural protein 5B polymerase inhibitor, sofosbuvir.⁸⁻¹¹ According to the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, boceprevir or telaprevir in combination with peg interferon alfa and ribavirin is the recommended treatment for patients with genotype 1 chronic hepatitis C.^{3,4} Treatment guidelines were published prior to the availability of simeprevir and sofosbuvir and do not address the place in therapy of these two agents. Overall, treatment guidelines do not give preference to one specific peg interferon or ribavirin product over another.²⁻⁷ Furthermore, no one protease inhibitor is preferred over another and current recommendations for their use are in line with Food and Drug Administration (FDA)-approved indications and dosing.²⁻¹⁰

Included in this review are the hepatitis C protease inhibitors boceprevir (Victrelis[®]), simeprevir (Olysio[®]), and telaprevir (Incivek[®]). All three agents are FDA-approved for the treatment of adults with chronic hepatitis C genotype 1 infection, when used in combination with peg interferon alfa and ribavirin. The agents can be used in treatment-naïve and experienced patients, and the specific FDA-approved indications are outlined in Table 2. These direct acting antivirals inhibit the replication of HCV host cells by binding to the NS3/4A protease of HCV genotype 1a and 1b.⁸⁻¹⁰ In general, clinical trials demonstrate that the use of protease inhibitors, in combination with peg interferon alfa and ribavirin, yields higher SVR rates, with a potential to decrease the total duration of treatment (24 [telaprevir], 28 [boceprevir] or 36 [boceprevir] compared to 48 weeks [standard of care]) in patients who achieve an early virologic response. The treatment duration with simeprevir in combination with peg interferon alfa and ribavirin is either 24 or 48 weeks depending on the response to prior treatment. In clinical trials, use of protease inhibitors was associated with a greater incidence of rash compared to the standard of care.^{2,4,10,13-22} In contrast to boceprevir or telaprevir combination therapy, simeprevir combination therapy was not associated with additional anemia compared to the standard of care.⁸⁻¹⁰

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Boceprevir (Victrelis [®])	Hepatitis C protease inhibitor	-
Simeprevir (Olysio [®])	Hepatitis C protease inhibitor	-
Telaprevir (Incivek [®])	Hepatitis C protease inhibitor	-

Indications

Table 2. Food and Drug Administration Approved Indications⁸⁻¹⁰

Indication	Boceprevir	Simeprevir	Telaprevir
Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders and relapsers	✓	✓	✓

There are additional factors that should be considered before initiating therapy with protease inhibitors. These agents should never be used as monotherapy and should only be used in combination with peg interferon alfa and ribavirin. The efficacies of protease inhibitors have not been evaluated in patients who have previously failed therapy with a treatment regimen that includes hepatitis C virus (HCV) nonstructural protein (NS) 3/4A protease inhibitors.⁸⁻¹⁰

With regard to boceprevir-containing regimens, efficacy in patients documented to be historical null responders (<2 log₁₀ HCV ribonucleic acid decrease by treatment week 12) during prior therapy with peg interferon alfa and ribavirin has been evaluated in the currently ongoing and unpublished study, PROVIDE, though a high proportion of previous null responders did not achieve a sustained virologic response (SVR). Poorly interferon responsive patients treated with a boceprevir-containing regimen have a lower likelihood of achieving a SVR, and a higher rate of detection of resistance-associated substitutions upon treatment failure, compared to patients with a greater response to peg interferon alfa and ribavirin.⁸

With regard to simeprevir-containing regimens, the efficacy in combination with peg interferon alfa and ribavirin is influenced by baseline host and viral factors. The efficacy is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to patients infected with HCV genotype 1a without the Q80K polymorphism. Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.¹⁰

With regard to telaprevir-containing regimens, a high proportion of previous null responders, particularly those with cirrhosis, did not achieve a SVR and had telaprevir resistance-associated substitutions emerge on treatment with telaprevir-containing regimens.⁹

Pharmacokinetics

Table 3. Pharmacokinetics¹²

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Boceprevir	Not reported	9	None	3.4
Simeprevir	Not reported	<1	None	41
Telaprevir	Not reported	1	R diastereomer*	9 to 11

*30-fold less active compared to telaprevir.

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the hepatitis C protease inhibitors are outlined in Table 4. Data from clinical trials support the Food and Drug Administration (FDA)-approved indications and dosing recommendations for these agents. Overall, the addition of hepatitis C protease inhibitors to standard therapy (i.e., peg interferon alfa and ribavirin) is associated with a significant increase in sustained virologic response (SVR) (undetectable hepatitis C virus [HCV] ribonucleic acid [RNA] levels 24 weeks after completion of treatment) rates. The addition of these agents to standard therapy is also associated with a higher incidence

of adverse events, such as rash.¹³⁻²² In contrast to boceprevir or telaprevir combination therapy, simeprevir combination therapy was not associated with additional anemia compared to the standard of care.¹⁰

Based on the FDA-approved dosing for boceprevir, patients are required to initiate standard therapy for a period of four weeks before initiating treatment with boceprevir.⁸ This is based on phase 2 trial data in which it was determined that in order to decrease the rate of viral breakthrough and relapse in patients receiving boceprevir, HCV RNA levels should be lowered as much as possible before initiation of boceprevir.²²

Poordad et al evaluated the safety and efficacy of boceprevir, in combination with standard therapy, in treatment-naïve adults with chronic HCV genotype 1 infection (SPRINT-2; N=1,097). Patients were excluded if they were co-infected with human immunodeficiency virus (HIV) or hepatitis B. There were three treatment regimens (control [i.e., standard therapy], response-guided therapy and fixed duration therapy), all of which included a four week lead-in period consisting of only standard therapy. Of note, self-described nonblack and black patients were enrolled into two separate cohorts due to the marked difference in rates of SVR between these two populations (nonblack; N=938, black; N=159). The control regimen consisted of an additional 44 weeks of standard therapy (48 weeks of treatment total). Response-guided therapy consisted of 24 weeks of boceprevir plus standard therapy, at which point if a rapid virologic response (undetectable HCV RNA at treatment week eight through 24) was achieved, treatment was considered complete (28 weeks of treatment total). However, if a rapid virologic response was not achieved, standard therapy alone was continued for an additional 20 weeks (48 weeks of treatment total). Fixed duration therapy consisted of 44 weeks of boceprevir plus standard therapy (48 weeks of treatment total). All patients were followed for a total of 72 weeks, which included either 24, 44 or 48 weeks of follow up, depending on total treatment duration.

For SPRINT-2, the primary efficacy endpoint of SVR was significantly higher with response-guided and fixed duration therapies (i.e., boceprevir-containing regimens) among the nonblack and black cohorts, compared to control. Specifically, within the nonblack cohort, SVR rates were 40 (N=311), 67 (N=316) and 68% (n =311) with control, response-guided therapy and fixed duration therapy ($P<0.001$ vs control for both). Within the black cohort, the corresponding rates were 23 (N=52), 42 (N=52) and 53% (N=55) ($P=0.04$ vs control for response-guided therapy and $P=0.004$ vs control for fixed duration therapy).¹³

Subgroup analyses of SPRINT-2 revealed that regardless of the degree of HCV RNA decrease from baseline after a four week lead-in period with standard therapy (<1 or ≥ 1 \log_{10} IU/mL), the addition of boceprevir was consistently more likely to result in SVR compared to standard therapy alone. Overall, however, a decrease of <1 \log_{10} IU/mL (poor interferon response) was associated with lower SVR rates and higher rates of boceprevir-resistance-associated variants. In addition, the SVR rates among patients with undetectable HCV RNA levels at treatment week eight were high regardless of treatment regimen; however, patients receiving boceprevir-containing regimens were three times more likely to achieve this early virologic response compared to patients receiving standard therapy alone. With regard to response-guided and fixed duration therapies, SVR rates within the nonblack cohort were similar (67 vs 68%; P value not reported), whereas within the black cohort they were higher with fixed duration therapy (42 vs 53%; P value not reported). Furthermore, among nonblack patients treated with a boceprevir-containing regimen who had an early virologic response (HCV RNA level undetectable at treatment week eight) (60%), and those who remained undetectable through 24 weeks of treatment (47%), the SVR rate was similar between response-guided (24 weeks of boceprevir) and fixed duration (44 weeks of boceprevir) therapies (97 vs 96%; P value not reported). Similar SVR rates between response-guided and fixed duration therapies were also observed among patients who did not have an early response (74% for each). Fatigue, headache and nausea were the most common adverse events reported in all treatment groups, with dysgeusia and anemia occurring more frequently with boceprevir-containing regimens.¹³

Results from SPRINT-2 demonstrated that the addition of boceprevir to standard therapy significantly increased the SVR rate among treatment-naïve adult patients with chronic HCV genotype 1 infection, with an increased incidence of anemia. The data also supports the efficacy of response-guided therapy, which consisted of individualized treatment duration based on HCV RNA levels between treatment weeks eight and 24.¹³

Bacon et al evaluated the safety and efficacy of boceprevir, in combination with standard therapy, in treatment-experienced adult patients with chronic HCV genotype 1 infection (RESPOND-2, N=403). In this trial, patients had to have demonstrated previous responsiveness to interferon based therapy (minimum of 12 weeks), but experienced either a nonresponse (decrease in the HCV RNA level $\geq 2 \log_{10}$ IU/mL by treatment week 12 of prior therapy, but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR) or relapse (undetectable HCV RNA level at the end of prior therapy without subsequent attainment of a SVR). RESPOND-2 and SPRINT-2 were similar in design in that patients co-infected with HIV or hepatitis B were excluded, there were three treatment regimens (control [N=80], response-guided therapy [N=162] and fixed duration therapy [N=161]) and all treatment regimens consisted of a four week lead-in period with standard therapy alone. In contrast, RESPOND-2 did not separate nonblack and black patients and, as mentioned previously, patients were treatment-experienced. Similar to SPRINT-2, the control regimen consisted of standard therapy for an additional 44 weeks (48 weeks of total treatment) and the fixed duration therapy consisted of boceprevir plus standard therapy for 44 weeks (48 weeks of total treatment). Response-guided therapy consisted of boceprevir plus standard therapy for 32 weeks, if at which point HCV RNA levels were undetectable at treatment weeks eight and 12, treatment was considered complete (36 weeks of total treatment). However, if the HCV RNA level was detectable at treatment week eight and undetectable at treatment week 12, standard therapy alone was continued for an additional 12 weeks (48 weeks of total treatment). All patients were followed for a total of 72 weeks which included either 24, 36 or 60 weeks of follow up, depending on treatment duration.¹⁷

For RESPOND-2, the primary efficacy endpoint of SVR was again significantly higher with response-guided and fixed duration therapies (i.e., boceprevir-containing regimens) compared to control. Specifically, SVR rates were 21, 59 and 66% with control, response-guided therapy and fixed duration therapy, respectively ($P < 0.001$ vs control for both). Among the two subgroups of treatment-experienced patients, those with a prior relapse (29, 69 and 75% with control, response-guided and fixed duration therapies, respectively) or prior nonresponse (7 vs 40 and 52%, respectively) both had higher SVR rates with boceprevir-containing regimens compared to standard therapy alone. With regards to response-guided and fixed dose therapies, no difference was observed in overall SVR rates (odds ratio, 1.4; 95% confidence interval [CI], 0.9 to 2.2). In addition, of the patients who responded poorly to therapy (HCV RNA level decrease $< 1 \log_{10}$ IU/mL at treatment week four), SVR was more likely to be achieved with boceprevir-containing regimens compared to standard therapy alone (0 vs 33 and 34%, respectively; P values not reported) and similar results were observed among good responders (HCV RNA level decrease $\geq 1 \log_{10}$ IU/mL) (25 vs 73 and 79%, respectively; P values not reported). The proportions of patients who achieved an early response (undetectable HCV RNA level at treatment week eight), were 46 and 52% with response-guided and fixed duration therapies, respectively, which was approximately six times higher compared to control (9%). Serious adverse events and anemia were reported more frequently with boceprevir-containing regimens.¹⁷

Results from RESPOND-2 demonstrated that the addition of boceprevir to standard therapy significantly increased the SVR rate among treatment-experienced adult patients with chronic HCV genotype 1 infection. The data also suggested that boceprevir-containing regimens may be more effective in achieving SVR in patients with a previous relapse (69 to 75%) compared to those who experienced a nonresponse to previous therapy (40 to 52%). Similar to SPRINT-2, achievement of an early virologic response resulted in similar SVR rates with response-guided therapy (32 weeks of boceprevir) and fixed duration therapy (44 weeks of boceprevir), further supporting the notion that patients who respond early to treatment with a boceprevir-containing regimen may be appropriate for a shorter duration of total treatment.¹⁷

Most trials with boceprevir have evaluated its use in combination with peg interferon alfa 2b, but Flamm et al evaluated the efficacy of boceprevir in combination with peg interferon alfa 2a and ribavirin in patients who were relapsers or nonresponders to prior therapy. Rates of SVR were significantly higher with boceprevir-containing regimens compared to placebo, with overall SVR rate of 21% in the peg interferon/ribavirin only treatment group compared to an SVR rate of 64% with boceprevir ($P < 0.001$). Rates of SVR among patients with a history prior relapse were 70% with boceprevir and 28% with peg interferon/ribavirin only treatment group, while SVR rates among patients with prior nonresponse were 47% with boceprevir compared to 5% in the peg interferon/ribavirin only treatment group (P values not reported).²⁰

Most recently, boceprevir has been studied in patients documented to be historical null responders ($<2 \log_{10}$ HCV ribonucleic acid decrease by treatment week 12) with prior therapy consisting of peg interferon alfa and ribavirin in a currently ongoing and unpublished study, though preliminary data has been released permitting a labeling update to expand its indication to include the treatment of prior null responders. The PROVIDE is an ongoing, open-label, single-arm study of adult subjects with HCV genotype 1 infection who did not achieve SVR while in the peg interferon alfa/ribavirin control arms of previous Phase 2 and 3 studies. Subjects who were prior null responders received a four week peg interferon alfa/ribavirin lead-in treatment followed by boceprevir 800 mg three times daily and peg interferon alfa/ribavirin for 44 weeks. Overall, 38% (20/52) achieved SVR, and the relapse rate was 14% (3/22) among the null responders.⁸

Based on the FDA-approved dosing of telaprevir, patients can initiate triple therapy (i.e., telaprevir plus standard therapy) at the same time. In contrast to boceprevir, lead-in period with standard therapy is not required before initiation of telaprevir.⁹

Jacobson et al evaluated the safety and efficacy of telaprevir, in combination with standard therapy, in treatment-naïve adult patients with chronic HCV genotype 1 infection (ADVANCE; N=1,088). Patients were excluded if they had decompensated liver disease, liver disease from other causes or hepatocellular carcinoma. There were three treatment regimens (control [N=361] and two response-guided therapies [N=727]). The control regimen consisted of 48 weeks of standard therapy (48 weeks of total treatment). The two response-guided therapies were T12/PR (N=363) and T8/PR (N=364). T12/PR consisted of telaprevir plus standard therapy for 12 weeks, and depending on whether or not an extended rapid virologic response (undetectable HCV RNA at treatment week four that remained undetectable at week 12) was achieved or not, standard therapy was continued for an additional 12 (24 weeks of treatment total) or 36 weeks (48 weeks of total treatment). T8/PR consisted of telaprevir plus standard therapy for eight weeks, followed by standard therapy alone for an additional four weeks. At which point, depending on whether or not an extended rapid virologic response was achieved, standard therapy alone was administered for an additional 12 (24 weeks of treatment total) or 36 weeks (48 weeks of treatment total). All patients were followed for a total of 72 weeks.¹⁴ For ADVANCE, the primary efficacy endpoint of SVR was significantly higher with both response-guided therapies (75 [$P<0.0001$ vs control], 69 [$P<0.0001$ vs control] and 44% with T12/PR, T8PR and control, respectively), with no difference observed between T12/PR and T8/PR (treatment difference, 6%; 95% CI, -12.5 to 0.6). When the results were analyzed according to extended rapid virologic response, fibrosis stage or race, SVR rates were consistently higher with telaprevir-containing regimens; however, comparisons were not always significant compared to control. Data suggests that 12 weeks of telaprevir may be more effective than eight weeks. Specifically, 12 weeks of telaprevir resulted not only in a nonsignificantly higher SVR rate, but also in a lower virologic failure rate (8 vs 13%; P value not reported). The difference in the rate of virologic failure was noted to be due to a higher failure rate in patients after telaprevir was discontinued. Beyond week 12, the rates of virologic failure were higher with T8PR compared to T12PR (10 vs 5%, respectively), with more frequent emergence of wild-type and lower-level resistant variants. Adverse events were reported more frequently with telaprevir-containing regimens included pruritis, nausea, rash, anemia and diarrhea.^{14,22}

Results from ADVANCE demonstrated that the addition of telaprevir to standard therapy significantly increased the SVR rate among treatment-naïve adult patients with chronic HCV genotype 1 infection, with an increased incidence of both rash and anemia. The data also demonstrated that 12 weeks of telaprevir is more efficacious than eight weeks.¹⁴

Sherman et al also evaluated the safety and efficacy of telaprevir, in combination with standard therapy, in treatment-naïve adult patients with chronic HCV genotype 1 infection (ILLUMINATE; N=540). In contrast to the other clinical trials, ILLUMINATE was an open-label, noninferiority trial. In this trial, patients were excluded if they were co-infected with HIV or hepatitis B. All patients received telaprevir plus standard therapy for 12 weeks, followed by standard therapy alone for an additional eight weeks. If at treatment week 20, an extended rapid virologic response was not achieved; standard therapy alone was administered for an additional 28 weeks (48 weeks of total treatment). If at treatment week 20 an extended rapid virologic response was achieved, standard therapy was administered for either an additional four (T12/PR24, 24 weeks of total

treatment) or 28 weeks (T12PR48, 48 weeks of total treatment). Patients were followed for a total of 72 weeks.¹⁵

In the ILLUMINATE trial, similar proportions of patients achieved the primary efficacy endpoint of SVR with T12PR24 compared to T12PR48 (92 vs 88%; 95% CI, -2 to 11; *P* value not reported). Overall, 332 patients achieved an extended rapid virologic response, of which 162 and 160 were randomly assigned to T12PR24 and T12PR48, respectively. The SVR rate among patients who did not achieve an extended rapid virologic response (N=118) was 64%.^{15,22}

Results from ILLUNIMATE support the concept that select patients who achieve an early virologic response with telaprevir-containing regimens may be candidates for a shorter duration of total treatment.¹⁵

Zeuman et al evaluated the safety and efficacy of telaprevir, in combination with standard therapy, in treatment-experienced adult patients with chronic HCV genotype 1 infection (REALIZE; N=662). Patients in this trial consisted of prior relapsers (undetectable HCV RNA level at the end of prior therapy without subsequent attainment of a SVR), partial responders (decrease in HCV RNA level $\geq 2 \log_{10}$ IU/mL by treatment week 12 of prior therapy, but not achieving HCV RNA undetectable status at the end of prior therapy), and null responders (decrease in HCV RNA level $< 2 \log_{10}$ IU/mL at treatment week 12 of prior therapy). There were three treatment regimens evaluated in the REALIZE trial (control, lead-in therapy and nonlead-in therapy). The control regimen consisted of standard therapy for 48 weeks (48 weeks of total treatment). The lead-in regimen (Lead-in T12PR48) consisted of standard therapy for four weeks, followed by telaprevir plus standard therapy for an additional 12 weeks, followed by standard therapy alone for an additional 32 weeks (48 weeks total of treatment). The non-lead-in regimen (T12PR48) consisted of telaprevir plus standard therapy for 12 weeks, followed by standard therapy alone for an additional 36 weeks (48 weeks of total treatment). All patients were followed for a total of 72 weeks.¹⁸

In the REALIZE trial, the primary efficacy endpoint of SVR was significantly higher with both telaprevir-containing regimens (66 [*P*<0.001 vs control], 64 [*P*<0.001 vs control] and 17% with lead-in T12PR48, T12PR48 and control), with no difference observed between lead-in T12PR48 and T12PR48 (*P* value not reported). Among the various subpopulations of treatment-experienced patients, SVR rates were consistently significantly higher with telaprevir-containing regimens (*P*<0.0001 for all comparisons). Subgroup analyses according to the stage of liver fibrosis or baseline viral load showed higher SVR rates with telaprevir-containing regimens compared to control. Reported adverse events were consistent with those described in other clinical trials evaluating telaprevir.^{18,22}

Results from REALIZE demonstrated that the addition of telaprevir to standard therapy significantly increased the SVR rate among treatment-experienced adult patients with chronic HCV genotype 1 infection. The data also supports the FDA-approved dosing of telaprevir in that no lead-in period is required and patients can initiate triple therapy at the same time.¹⁸

The efficacy of simeprevir in patients with HCV genotype 1 infection was evaluated in four unpublished studies, including two Phase 3 trials in treatment-naïve patients (QUEST 1 and QUEST 2), one Phase 3 trial in patients who relapsed after prior interferon-based therapy (PROMISE) and one Phase 2b trial in patients who failed prior therapy with peg interferon alfa and ribavirin (including prior relapsers, partial and null responders) (ASPIRE).¹⁰

Patients in these trials had chronic hepatitis C with compensated liver disease (including cirrhosis) and HCV RNA $\geq 10,000$ IU/mL. In patients who were treatment-naïve and prior relapsers, the overall duration of treatment with peg interferon alfa and ribavirin in the Phase 3 trials was response-guided. In these patients, the planned total duration of HCV treatment was 24 weeks if the following on-treatment protocol-defined response-guided therapy criteria were met: HCV RNA < 25 IU/mL (detectable or undetectable) at week four and undetectable HCV RNA at week 12. Treatment stopping rules for HCV therapy were used to ensure that patients with inadequate on-treatment virologic response discontinued treatment in a timely manner.¹⁰

The primary end point, SVR, was defined as undetectable HCV RNA 24 weeks after the end of treatment (SVR24) in the Phase 2b trial and was defined as HCV RNA <25 IU/mL (detectable or undetectable) 12 weeks after the end of treatment (SVR12) in the Phase 3 trials.¹⁰

QUEST 1 (N=394) and QUEST 2 (N=391) were similarly designed, randomized, double-blind, placebo-controlled, two-arm, multicenter, Phase 3 trials evaluating the efficacy of simeprevir in treatment-naïve patients with HCV genotype 1 infection. All patients received simeprevir 150 mg once daily for 12 weeks or placebo, plus peg interferon alfa-2a (QUEST 1 and QUEST 2) or peg interferon alfa-2b (QUEST 2) and ribavirin, followed by 12 or 36 weeks of therapy with peg interferon alfa and ribavirin in accordance with the response-guided therapy criteria. Patients in the control groups received 48 weeks of peg interferon alfa-2a or -2b and ribavirin.^{10,23,24}

In the pooled analysis of QUEST 1 and QUEST 2, a greater proportion of patients in the simeprevir group achieved SVR12 compared to control group (80 vs 50%). Eighty eight percent of patients in the simeprevir group were eligible to shorten total treatment duration to 24 weeks; in these patients, the SVR12 rate was 88%. SVR12 rates were higher in the simeprevir group compared to control group regardless of the fibrosis stage (84 vs 55% for F0 to F2 and 68 vs 36% for F3 to 4), sex, age, race, body mass index, HCV genotype/subtype, baseline HCV RNA load, and IL28B genotype. In the simeprevir group, SVR12 rates were lower in patients with genotype 1a virus with the NS3 Q80K polymorphism at baseline (58%) compared to those without the Q80K polymorphism (84%). The corresponding SVR12 rates in the control group were 52 and 43%, respectively.¹

The PROMISE trial (N=393) was a randomized, double-blind, placebo-controlled, two-arm, multicenter, Phase 3 trial in patients with HCV genotype 1 infection who relapsed after prior interferon-based therapy. All patients received simeprevir 150 mg once daily for 12 weeks or placebo, plus peg interferon alfa-2a and ribavirin, followed by 12 or 36 weeks of therapy with peg interferon alfa-2a and ribavirin in accordance with the response-guided therapy criteria. Patients in the control group received 48 weeks of peg interferon alfa-2a and ribavirin.^{1,25}

A greater proportion of patients in the simeprevir group achieved SVR12 compared to control group (79 vs 37%). Ninety three percent of patients in the simeprevir group were eligible to shorten total treatment duration of 24 weeks; in these patients, the SVR12 rate was 83%. SVR12 rates were higher in the simeprevir group compared to peg interferon alfa-2a and ribavirin group regardless of the fibrosis stage (82 vs 41% for F0 to F2 and 73 vs 24% for F3 to 4), sex, age, race, body mass index, HCV genotype/subtype, baseline HCV RNA load, prior HCV therapy, and IL28B genotype. In the simeprevir group, SVR12 rates were lower in patients with genotype 1a virus with the NS3 Q80K polymorphism at baseline (47%) compared to those without the Q80K polymorphism (78%). The corresponding SVR12 rates in the control group were 30 and 26%, respectively.¹

The ASPIRE trial (N=264) was a randomized, double-blind, placebo-controlled, seven-arm, Phase IIb trial in patients with HCV genotype 1 infection, who failed prior therapy with peg interferon alfa and ribavirin (including prior relapsers, partial responders or null responders). Patients received 12, 24 or 48 weeks of simeprevir 100 or 150 mg in combination with 48 weeks of peg interferon alfa-2a and ribavirin, or 48 weeks of placebo in combination with 48 weeks of peg interferon alfa-2a and ribavirin.^{1,26}

Overall, SVR24 rates were significantly higher in the groups treated with simeprevir 100 mg and 150 mg for 12 weeks compared to control (61 and 80% vs 23%; $P<0.001$). In the pooled results of simeprevir 100 mg and 150 mg given for 12 weeks, the SVR rates were significantly higher with simeprevir compared to placebo, regardless of prior response to peg interferon and ribavirin: prior null response, 45 vs 19%; prior partial response, 67 vs 9%; prior relapse, 83 vs 37%. In prior partial responders, SVR24 rates in the simeprevir treatment group were 47 and 77% in patients with HCV genotype 1a and 1b, respectively, compared to 13% and 7%, respectively, in the control group. In prior null responders, SVR24 rates in the simeprevir treatment group were 41 and 47% in patients with HCV genotype 1a and 1b, respectively, compared to 0 and 33%, respectively, in the control group. SVR24 rates were higher in the simeprevir group compared to control group, regardless of HCV genotype/subtype, fibrosis stage, and IL28B genotype.^{1,26}

The COSMOS trial is an ongoing, unpublished randomized, open-label, phase IIa trial evaluating a once daily combination of simeprevir 400 mg and sofosbuvir 150 mg with and without ribavirin for 12 and 24 weeks in HCV genotype 1 patients. The four-point score METAVIR scale was used to quantify the degree of inflammation and fibrosis of the liver. Cohort 1 (N=80) included prior null responders with METAVIR scores F0 to F2 and Cohort 2 (N=87) included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4. Only the results of an interim analysis are available at this time.²⁷

In the Cohort 1, SVR12 was achieved by 96% (26/27) of patients receiving a 12-week simeprevir added to sofosbuvir and ribavirin regimen and 93% (13/14) of patients receiving a 12-week simeprevir and sofosbuvir regimen without ribavirin. In the Cohort 2, SVR4 was achieved by 93% (14/15) of patients receiving a 12-week simeprevir added to sofosbuvir and ribavirin regimen and 100% (14/14) of patients receiving simeprevir and sofosbuvir regimen without ribavirin. Treatment was found to be generally safe and well tolerated. There was little to no benefit from adding ribavirin in this difficult to treat groups of hepatitis C patients and 12 week treatment provided similar clinical benefit to 24 week treatment.^{27,28}

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Genotype 1 Chronic Hepatitis: Treatment-Naïve Patients				
<p>Poordad et al¹³ SPRINT-2</p> <p>Group 1 (control): Peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks</p> <p>vs</p> <p>Group 2 (response-guided therapy): boceprevir 800 mg three times a day plus peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 24 weeks, followed by an additional 20 weeks of peg interferon alfa-2b plus ribavirin in detectable HCV RNA levels at any visit from week 8 to 24</p> <p>vs</p> <p>Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks</p> <p>All patients entered a 4 week lead in period in which peg interferon alfa-2b and ribavirin were administered.</p> <p>The trial consisted of two cohorts enrolling nonblacks and blacks</p>	<p>PC, PG, RCT</p> <p>Patients ≥18 years of age with a history of no previous treatment for HCV infection, weight 40 to 125 kg, chronic infection with HCV genotype 1 and plasma HCV RNA level ≥10,000 IU/mL</p>	<p>N=1,097 (N=938 [nonblack], N=159 [black])</p> <p>48 weeks (plus 24 weeks of follow up)</p>	<p>Primary: SVR, safety</p> <p>Secondary: Not reported</p>	<p>Primary: Among nonblack patients, the rate of SVR was 40, 67 and 68% in Groups 1, 2 and 3 ($P<0.001$ vs Group 1 for both Group 2 and 3). The corresponding numbers in black patients were 23, 42 ($P=0.04$ vs Group 1) and 53% ($P=0.004$ vs Group 1). Subgroup analyses revealed that at four weeks, 23 and 38% of nonblack and black patients had a decrease of $<1 \log_{10}$ IU/mL in HCV RNA level from baseline, which was associated with lower rates of SVR and higher rates of boceprevir-resistance-associated variants compared to those achieving a decrease of $\geq 1 \log_{10}$ IU/mL from baseline. However, regardless of the degree of reduction achieved at week four, patients receiving boceprevir achieved consistently higher rates of SVR compared to patients who received control overall.</p> <p>Adverse events occurred in more than 98% of all patients, with serious adverse events in 9, 11 and 12% of patients in Groups 1, 2 and 3, respectively. There were six deaths during the trial; four deaths in Group 1 and two deaths from boceprevir-containing regimens. Two suicides (one in Group 1 and one in Group 2) were determined to have possibly been related to treatment with peg interferon. Fatigue, headache and nausea were the most commonly reported adverse events. The incidence of dysgeusia was higher with boceprevir treatment. Anemia was reported in 29 and 49% of patients receiving control and boceprevir, respectively. Overall, 13 and 21% of control- and boceprevir-treated patients required dose reductions because of anemia and erythropoietin was administered in 24 and 43% of patients. Neutropenia and thrombocytopenia also occurred more frequently with boceprevir treatment.</p> <p>Secondary: Not reported</p> <p>Response rates at the end of therapy (undetectable HCV RNA level at the time that the study therapy was discontinued) were significantly higher with boceprevir-containing regimens compared to the control regimen.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>separately.</p> <p>Treatment was considered complete in Group 2 if the HCV RNA level was undetectable from week 8 through week 24 (total duration, 28 weeks).</p> <p>In all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 24 based on futility rules; these patients then entered the follow up period.</p>				<p>Among nonblack patients, viral breakthrough (undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) occurred in one to two percent of all patients, regardless of treatment regimen. In addition, relapse rates (undetectable HCV RNA level at the end of treatment but a detectable HCV RNA level at some point during the follow up period) were lower with boceprevir compared to control. The numbers of events among black patients were too few to permit comparison between the treatment groups.</p>
<p>Jacobson et al¹⁴ ADVANCE</p> <p>Telaprevir 750 mg three times a day plus peg interferon alfa-2a 180 µg weekly and ribavirin 1,000 or 1,200 mg/day for 12 weeks, followed by an additional 12 or 36 weeks of peg interferon alfa-2a plus ribavirin based on HCV RNA levels weeks 4 and 12 (T12PR)</p> <p>vs</p> <p>telaprevir 750 mg three times a day plus peg interferon alfa-2a 180 µg weekly and ribavirin 1,000 or 1,200 mg/day for 8 weeks, followed by an additional 16 or 40 weeks of peg interferon alfa-2a plus ribavirin based on HCV RNA levels weeks 4 and 12 (T8PR)</p>	<p>DB, PC, PG, RCT</p> <p>Patients 18 to 70 years of age with chronic HCV genotype 1 infection with no previous treatment</p>	<p>N=1,088</p> <p>48 weeks (plus 24 weeks of follow up)</p>	<p>Primary: SVR</p> <p>Secondary: Proportion of patients with undetectable HCV RNA at week 72, four, 12 or both four and 12, at the end of treatment and 12 weeks after the last planned dose of treatment; safety</p>	<p>Primary: SVR rates were significantly higher with telaprevir-containing regimens compared to control (75, 69 and 44% with T12PR, T8PR and control ($P<0.001$ for T12PR and T8PR vs control).</p> <p>Secondary: Seventy three, 67 and 44% of patients receiving T12PR, T8PR and control had undetectable HCV RNA 72 weeks after starting treatment ($P<0.001$ for T12PR and T8PR vs control).</p> <p>Sixty eight, 66 and nine percent of patients, respectively, had undetectable HCV RNA at week four (rapid virologic response), and 58, 57 and eight percent of patients, respectively, had undetectable HCV RNA at weeks four and 12 (extended rapid virologic response) (P values not reported).</p> <p>Among patients with an extended rapid virologic response assigned to receive a total of 24 weeks of therapy, SVR rates were 89 and 83% with T12PR and T8PR (P value not reported).</p> <p>Among patients who had undetectable HCV RNA levels after the last dose of treatment, relapse rates were nine, nine and 28% with T12PR, T8PR and control (P values not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs</p> <p>peg interferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 48 weeks (control)</p> <p>Patients in the T12PR and T8PR groups who met criteria for an extended rapid virologic response (undetectable HCV RNA at weeks 4 and 12) received 12 additional weeks of treatment with peg interferon alfa-2a plus ribavirin (24 total weeks of treatment).</p> <p>Patients who had detectable HCV RNA either at week 4 or 12 received an additional 36 weeks of peg interferon alfa-2a plus ribavirin (48 total week of treatment).</p>				<p>Subgroup analyses demonstrated that SVR rates were higher with telaprevir-containing regimens. Subgroup analyses included HCV genotype subtype (1a and 1b), African Americans, baseline HCV RNA levels (≥800,000 IU) and bridging fibrosis or cirrhosis.</p> <p>The incidence of gastrointestinal disorders, pruritis, rash and anemia was ≥10 percentage points higher with telaprevir-containing regimens. A total of 10, 10 and seven percent of patients receiving T12PR, T8PR and control discontinued all treatment at some time during the trial owing to adverse events (<i>P</i> values not reported); with seven, eight and four percent of these patients discontinuing during the telaprevir (or placebo) phase. Anemia and rash were the most frequently reported adverse events that lead to discontinuation. One case of Stevens-Johnson syndrome occurred approximately 11 weeks after the last dose of telaprevir had been administered.</p>
<p>Sherman et al¹⁵ ILLUMINATE</p> <p>Peg interferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day plus telaprevir 750 mg three times a day for 12 weeks (T12PR12), followed by peg interferon alfa-2a plus ribavirin for 12 or 36 weeks.</p> <p>Patients who achieved an extended rapid virologic response (undetectable HCV RNA levels at weeks 4 and 12) after 20 weeks were randomized to continue peg interferon alfa-2a plus ribavirin for an</p>	<p>MC, NI, OL, RCT</p> <p>Patients 18 to 70 years of age with chronic hepatitis C genotype 1 infection for ≥6 months, no previous treatment and with no hepatitis B or HIV</p>	<p>N=540</p> <p>24 or 48 weeks (plus 24 weeks of follow up)</p>	<p>Primary: SVR in T12PR24 compared to T12PR48</p> <p>Secondary: Not reported</p>	<p>Primary: The absolute difference in SVR rate between T12PR24 vs T12PR48 was four percentage points (92 vs 88%; 95% CI, -2 to 11). The lower limit of this 95% CI (-2%) exclude the NI margin -10.5%. The SVR rate in patients who did not achieve an extended rapid virologic response therefore received a total of 48 weeks of treatment was 64% (76/118).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>additional 4 (24 weeks total treatment; T12PR24) or 28 weeks (48 total weeks of treatment; T12PR48).</p> <p>Patients who did not achieve an extended rapid virologic response after 20 weeks received peg interferon alfa-2a plus ribavirin for an additional 28 weeks (48 total weeks of treatment).</p>				
<p>Kumada et al¹⁶</p> <p>(Group A) Telaprevir 750 mg three times a day plus peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day (based on body weight) for 12 weeks, followed by an additional 12 weeks of peg interferon alfa-2a plus ribavirin</p> <p>vs</p> <p>(Group B) Peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day (based on body weight) for 48 weeks</p>	<p>AC, DB, MC, RCT</p> <p>Patients 20 to 65 years of age with chronic HCV genotype 1 infection who had not received prior treatment and had a current HCV RNA $\geq 5.0 \log_{10}$ IU/mL, no hematologic abnormalities and a weight of 40 to 120 kg</p>	<p>N=189</p> <p>24 or 48 weeks (plus 24 weeks of follow up)</p>	<p>Primary: SVR, nonresponder rate, proportion of patients with an RVR at week four, safety, and adverse events</p> <p>Secondary: Not reported</p>	<p>Primary: Treatment with telaprevir (Group A) was associated with a statistically significant increase in SVR rate (73.0 vs 49.2%; $P=0.0020$) compared to standard of care (Group B).</p> <p>The nonresponder rate was significantly lower in Group A (triple therapy) compared to Group B (0.8 vs 20.6%; $P<0.0001$).</p> <p>A higher proportion of women achieved an SVR in Group A compared to Group B (70.0 vs 43.3%; $P=0.0214$). In addition, patients ≥ 50 years of age achieved a significantly higher SVR in Group A compared to Group B (67.1 vs 42.9%; $P=0.0125$). Furthermore, more patients with a high HCV RNA viral load at baseline ($\geq 7 \log_{10}$ IU/ml) achieved a SVR in Group A compared to Group B (69.2 vs 27.8%; $P=0.0132$).</p> <p>A significantly greater proportion of patients achieved a RVR at four weeks in Group A compared to Group B (84.0 vs 4.8%; $P<0.0001$).</p> <p>The most commonly reported adverse events were anemia, pyrexia, leukocytopenia, thrombocytopenia and malaise. Drugs were discontinued due to adverse events in a similar number of patients in Groups A and B (16.7 vs 22.2%, respectively; P value not reported). Telaprevir was discontinued in 19.0% of patients in Group A.</p> <p>Anemia occurred in 91.3 and 73.0% of patients in Groups A and B,</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>respectively. Combined, Grade 1 and 2 anemia was more common in Group A compared to Group B (38.1 vs 17.5%; $P=0.0045$). Grade 3 anemia occurred in 11.1% in Group A only. During the follow-up, hemoglobin increased both in Groups A and B, and returned to pretreatment levels 12 weeks after the completion of therapy.</p> <p>Skin disorders occurred in a similar proportion of patients in Groups A and B (89.7 vs 84.1%, respectively; P value not reported). Most skin disorders were mild and categorized as Grade 1. Combined, skin disorders of Grades 2 to 4 occurred more frequently in Group A than Group B (46.8 vs 23.8%; $P=0.0026$). Serious skin disorders developed in three patients in Group A, but zero patients in Group B. Stevens-Johnson syndrome occurred in one patient after 35 days of treatment and led to the discontinuation of treatment.</p> <p>Secondary: Not reported</p>
Treatment of genotype 1 chronic hepatitis: Treatment-experienced patients				
<p>Bacon et al¹⁷ RESPOND-2</p> <p>Group 1 (control): Peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks</p> <p>vs</p> <p>Group 2 (response-guided therapy): boceprevir 800 mg three times a day plus peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 32 weeks, followed by an additional 12 weeks of peg interferon alfa-2b plus ribavirin in detectable HCV RNA levels at week 8 but undetectable at week 12</p>	<p>PC, PG, RCT</p> <p>Patients with chronic HCV genotype 1 infection who demonstrated responsiveness to interferon (minimum duration of therapy, 12 weeks)</p>	<p>N=403</p> <p>48 weeks (plus 24 weeks of follow up)</p>	<p>Primary: SVR, safety</p> <p>Secondary: Proportion of patients with an early response in whom a SVR was achieved, proportion of patients with a relapse</p>	<p>Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to control, with overall rates of SVR of 21, 59 and 66% in Groups 1, 2 and 3, respectively ($P<0.001$). The increase observed with Groups 2 and 3 was largely due to end of treatment rates of response being higher (70 and 77 vs 31%) and relapse rates being lower (15 and 12 vs 32%) compared to Group 1. The absolute difference between Groups 2 and 1 was 34.7 percentage points (95% CI, 25.7 to 49.1), and between Groups 3 and 1 it was 45.2 percentage points (95% CI, 33.7 to 56.8). There was no difference in SVR rates between Groups 2 and 3 (OR, 1.4; 95% CI, 0.9 to 2.2).</p> <p>Overall, the most common adverse events were flulike symptoms, while dysgeusia, rash and dry skin were more commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events, and there were more discontinuations and dose modifications due to adverse events with boceprevir. Anemia occurred more frequently with boceprevir (43 to 46 vs 20%), and erythropoietin was administered more frequently to patients receiving boceprevir.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs</p> <p>Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks</p> <p>All patients entered a 4 week lead in period in which peg interferon alfa-2b and ribavirin were administered.</p> <p>Treatment was considered complete in Group 2 if the HCV RNA level was undetectable at weeks 8 and 12 (total duration, 36 weeks).</p> <p>In addition, in all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 12 based on futility rules; these patients then entered the follow up period.</p>				<p>Secondary:</p> <p>The proportion of patients with an undetectable HCV RNA level at week eight in Groups 2 and 3 (46 and 52%) was approximately six times the proportion in Group 1 (9%). Early response was associated with a high rate of SVR in all three treatment groups (100, 86 and 88% in Groups 1, 2 and 3; <i>P</i> values not reported).</p> <p>The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 29, 69 and 75% in Groups 1, 2 and 3; respectively (<i>P</i> values not reported). And the patients with prior nonresponse (a decrease in the HCV RNA level of $\geq 2 \log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), the corresponding rates were 7, 40 and 52% (<i>P</i> values not reported).</p> <p>Virologic breakthrough (achievement of an undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) and incomplete virologic response (an increase of 1 \log_{10} IU/mL in the HCV RNA level from the nadir, with an HCV RNA level >1,000 IU/mL) were infrequent during the treatment period.</p> <p>Multivariable stepwise logistic-regression analysis served to identify five baseline factor that were significantly associated with achievement of a SVR: assignment to boceprevir (OR for Groups 2 and 3 vs Group 1, 7.3 and 10.7, respectively; <i>P</i><0.001 for both), previous relapse (OR vs previous nonresponse, 3.1; <i>P</i><0.001), low viral load at baseline (OR vs high load, 2.5; <i>P</i>=0.02) and absence of cirrhosis (OR vs presence, 2.1; <i>P</i>=0.04).</p>
<p>Zeuzem et al¹⁸ REALIZE</p> <p>Telaprevir 750 mg three times a day plus peg interferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day for 12 weeks, followed by an</p>	<p>DB, PC, RCT</p> <p>Patients 18 to 70 years of age with chronic HCV genotype 1 infection, no</p>	<p>N=662</p> <p>48 weeks (plus 24 weeks of follow up)</p>	<p>Primary: SVR</p> <p>Secondary: Effect of lead-in treatment with peg</p>	<p>Primary:</p> <p>Compared to control, SVR rates were significantly higher with telaprevir-containing regimens in patients who had a previous relapse (83, 88 and 24% with T12PR48, Lead-in T12PR48 and control), for those who did not have a previous virologic response (41, 41 and 9%), including those who had a partial response (59, 54 and 15%) and those who had no response (29, 33 and 5%) (<i>P</i><0.001 for all comparisons).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>additional 36 weeks of peg interferon alfa-2a plus ribavirin (T12PR48)</p> <p>vs</p> <p>peg interferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 4 weeks, followed by telaprevir 750 mg three times a day plus peg interferon alfa-2a 180 µg weekly and ribavirin 1,000 to 1,200 mg/day for 12 weeks, followed by an additional 32 weeks of peg interferon alfa-2a plus ribavirin (Lead-in T12PR48)</p> <p>vs</p> <p>peg interferon alfa-2a 180 µg weekly and ribavirin 1,000 to 1,200 mg/day for 48 weeks (control)</p> <p>Patients could have 1 of 3 previous responses to peg interferon alfa plus ribavirin therapy; no response (reduction <2 log₁₀ in HCV RNA after 12 weeks of therapy), partial response (reduction ≥2 log₁₀ in HCV RNA after 12 weeks of therapy but with detectable HCV RNA) or relapse (undetectable HCV RNA at the end of a previous course of therapy with HCV RNA positivity thereafter).</p>	<p>SVR to 1 previous course of peg interferon alfa and ribavirin despite receiving at least 80% of the intended dose</p>		<p>interferon alfa-2a plus ribavirin on SVR, proportion of patients who had undetectable HCV RNA at four and eight weeks, relapse, change from baseline in log₁₀ HCV RNA, safety</p>	<p>SVR rates were similar with T12PR48 and Lead-in T12PR48 among patients who had a relapse or no response or a partial response to previous therapy (<i>P</i> values not reported).</p> <p>Secondary: Overall, SVR rates were 64, 66 and 17% with T12PR48, Lead-in T12PR48 and control. Differences was 47 percentage points between T12PR48 and control (95% CI, 37 to 57; <i>P</i><0.001) and 50 percentage points between Lead-in T12PR48 and control (95% CI, 40 to 60; <i>P</i><0.001).</p> <p>In patients with a previous relapse, the proportion of patients with an undetectable HCV RNA were 70 and 93, three and 89 and three and 10% with T12PR48, Lead-in T12PR48 and control (<i>P</i> values not reported). In patients with a previous partial response, the corresponding proportions were 65 and 82, zero and 65 and zero and zero percent (<i>P</i> values not reported).</p> <p>Relapse rates were lower with telaprevir-containing regimens among patients who had a previous relapse or no response or a partial response to previous therapy.</p> <p>Changes in log₁₀ HCV RNA levels are provided in graphic form only.</p> <p>The most frequently reported adverse events (>25% of patients) with telaprevir were fatigue, pruritus, rash, nausea, influenza-like illness, anemia and diarrhea. Serious adverse events (12 vs 5%) and those leading to treatment discontinuation (13 vs 3%) were more frequent with telaprevir.</p>
<p>Hayashi et al¹⁹</p> <p>Telaprevir 750 mg three times a day</p>	<p>MC, OL</p> <p>Patients 20 to</p>	<p>N=141 (109 relapsers</p>	<p>Primary; SVR, relapse,</p>	<p>Primary: The SVR rate was 88.1% (96/109) in patients who were prior relapsers to treatment and 34.4% in patients who were previous nonresponders to</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>plus peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day (based on body weight) for 12 weeks, followed by an additional 12 weeks of peg interferon alfa-2a plus ribavirin</p>	<p>65 years of age with chronic HCV genotype 1 infection who were relapsers or nonresponders to a previous course of peg interferon alfa and ribavirin with a current HCV RNA ≥ 5.0 log₁₀ IU/mL, no hematologic abnormalities and a weight of 40 to 120 kg</p>	<p>and 32 non-responders)</p> <p>24 weeks (plus 24 weeks of follow up)</p>	<p>breakthrough, nonresponse, and safety</p> <p>Secondary: Not reported</p>	<p>treatment 34.4% (11/32).</p> <p>The RVR and ETR rates in prior relapsers were 87.2% (95/109) and 94.5% (103/109), respectively (P values not reported). In prior nonresponders, the RVR and ETR rates were 71.9% (23/32) and 59.4% (19/32), respectively.</p> <p>In prior relapsers, the SVR rate in the patients who achieved undetectable HCV RNA at week four was significantly higher compared to patients achieving undetectable HCV RNA after week four of treatment (91.8 vs 66.7%; $P=0.0487$). In the prior nonresponder group, undetectable HCV RNA at week four did not appear to have an effect on SVR rates (39.1 vs 28.6%; $P=1.0$).</p> <p>The SVR rate in previous relapsers was significantly higher in males compared to females (93.9 vs 79.1%; $P=0.0316$), while there was no difference in SVR rate between genders in patients who were previous nonresponders to therapy.</p> <p>The rates of nonresponse, breakthrough and relapse were 0.9% (1/109), 0.9% (1/109) and 7.3% (8/109), respectively, in patients who were prior relapsers. The incidence of nonresponse, breakthrough and relapse in prior nonresponders was 6.3% (2/32), 18.8% (6/32) and 40.6% (13/32), respectively.</p> <p>The incidence of adverse events was similar between the prior relapsers and prior nonresponders. Serious adverse events were reported in 11.9% (13/109) of prior relapsers and 9.4% (3/32) of prior nonresponders. Overall, the most frequently reported adverse events in prior relapsers and prior nonresponders were anemia (88.1 vs 100%, respectively), pyrexia (82.6 vs 93.8%, respectively), decreased white blood cell count (76.1 vs 69.8%, respectively), blood uric acid increase (66.1 vs 78.1%, respectively) and platelet count decrease (67.0 vs 68.6%, respectively).</p> <p>Overall, 17.4% of prior relapsers discontinued treatment due to adverse events compared to 12.5% of prior nonresponders. Anemia was the most frequently reported adverse event leading to discontinuation in both</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>treatment groups.</p> <p>Adverse events related to skin disorders were observed in 82.3% (116/141) of patients. Skin disorders reported in over 10% of the patients were rash 39.0% (55/141), drug eruption in 24.1% (34/141), injection site reaction in 12.8% (18/141) and injection site erythema in 12.8% (18/141) of the patients.</p> <p>Despite ribavirin dose modification, the median hemoglobin levels in prior relapsers and prior nonresponders decreased to 10.6 and 10.4 g/dL at week 12, respectively. No patient discontinued all the study drugs because of a neutrophil decrease.</p> <p>Secondary: Not reported</p>
<p>Flamm et al²⁰</p> <p>Peg interferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day plus placebo for 48 weeks total</p> <p>vs</p> <p>boceprevir 800 mg three times a day plus peg interferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 44 weeks (total treatment duration of 48 weeks)</p> <p>All patients entered a 4 week lead in period in which peg interferon alfa-2a and ribavirin were administered.</p> <p>In addition, in all treatment groups, treatment was discontinued for all patients with a detectable HCV RNA</p>	<p>PC, PG, RCT</p> <p>Patients with chronic HCV genotype 1 infection who were relapsers or nonresponders to a previous course of peg interferon alfa and ribavirin</p>	<p>N=201</p> <p>48 weeks (plus 24 weeks of follow up)</p>	<p>Primary: SVR</p> <p>Secondary: Proportion of patients whom a SVR was achieved by prior response (relapse and nonresponse), safety</p>	<p>Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to placebo, with overall rates of SVR of 21% in the peg interferon/ribavirin only treatment group compared to and SVR rate of 64% with boceprevir (P<0.001).</p> <p>Secondary: The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 28% in the peg interferon/ribavirin only treatment group compared to and SVR rate of 70% with boceprevir (P values not reported).</p> <p>The rates of SVR among patients with prior nonresponse (a decrease in the HCV RNA level of $\geq 2 \log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), were 5% in the peg interferon/ribavirin only treatment group compared to and SVR rate of 47% with boceprevir (P values not reported).</p> <p>Overall, the most common adverse events were flulike symptoms, while dysgeusia, diarrhea, rash, myalgia, leukopenia and vomiting were more</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
level at week 12 based on futility rules; these patients then entered the follow up period.				<p>commonly reported with boceprevir-containing regimens.</p> <p>A greater proportion of patients receiving boceprevir reported serious adverse events (13 vs 10%), and there were more discontinuations (17 vs 3%) and dose modifications (43 vs 22%) due to adverse events with boceprevir.</p> <p>Anemia occurred more frequently with boceprevir (50 vs 57%). Anemia was managed with dose reduction in 8% of control group and 0% in the boceprevir group. Erythropoietin was administered more frequently to patients receiving boceprevir (28 vs 29%) and a combination of both interventions in 56% of the placebo group and 57% of the boceprevir group). Neutropenia occurred more frequently with boceprevir (31 vs 18%), and granulocyte colony-stimulating factor administered more frequently with boceprevir (14 vs 12%).</p> <p>Secondary: Not reported</p>

Study abbreviations: CI=confidence interval, DB=double blind, MC=multicenter, NI=non-inferiority, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial

Miscellaneous abbreviations: ETR=end of treatment response, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IU=international units, RNA=ribonucleic acid, RVR=rapid viral response, SVR=sustained virologic response

Special Populations**Table 5. Special Populations**⁸⁻¹⁰

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Boceprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	B*	Unknown; use with caution.
Simeprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild impairment; safety and efficacy in moderate to severe hepatic impaired have not been established.	C*	Unknown; use with caution.
Telaprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild impairment; use is not recommended in moderate to severe impairment.	B*	Unknown; use with caution.

*Ribavirin has a pregnancy category of X. Boceprevir, simeprevir, and telaprevir must be used in combination with ribavirin and peg interferon alfa.

Adverse Drug Events

The adverse events reported in clinical trials for boceprevir (regardless of causality) with a frequency $\geq 10\%$ of patients receiving boceprevir in combination with peg interferon and ribavirin, and reported at a rate $\geq 5\%$ than peg interferon and ribavirin alone are outlined in Table 6. In addition, adverse events reported in clinical trials for simeprevir or telaprevir, in combination with peg interferon and ribavirin, with a frequency $\geq 3\%$ and $\geq 5\%$ higher, respectively, compared to peg interferon and ribavirin alone are also outlined in Table 6.⁸⁻¹⁰

Table 6. Adverse Drug Events (%)⁸⁻¹⁰

Adverse Event(s)	Boceprevir*	Simeprevir	Telaprevir
Blood and Lymphatic System Disorders			
Anemia	50/45	-	36
Neutropenia	25/14	-	-
Central Nervous System			
Dizziness	19/16	-	-
Insomnia	34/30	-	-
Irritability	22/21	-	-
Gastrointestinal			
Anorectal discomfort	-	-	11
Diarrhea	25/24	-	26
Dry mouth	11/15	-	-
Dysgeusia	35/44	-	10
Hemorrhoids	-	-	12
Nausea	46/43	22	39

Adverse Event(s)	Boceprevir*	Simeprevir	Telaprevir
Vomiting	20/15	-	13
General Disorders and Administration Site Conditions			
Asthenia	15/21	-	-
Chills	34/33	-	-
Fatigue	58/55	-	56
Metabolism and Nutrition Disorders			
Decreased appetite	25/26	-	-
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	19/23	-	-
Myalgia	-	16	-
Respiratory			
Dyspnea, including exertional dyspnea	-	12	-
Dyspnea, exertional	8/11	-	-
Skin and Subcutaneous Tissue Disorders			
Alopecia	27/22	-	-
Dry skin	18/22	-	-
Pruritis	-	22	47
Rash	17/16	28	56

- Event not reported or incidence <1%.

*Reported as: treatment-naïve patients/previous treatment failures (percent/percent).

Contraindications/Precautions

The hepatitis C protease inhibitors are contraindicated in women who are or who may become pregnant and in men whose female partners are pregnant because of the risk for birth defects and fetal death associated with ribavirin.⁸⁻¹⁰

Boceprevir and telaprevir are contraindicated when combined with drugs that are highly dependent on cytochrome P450 (CYP) 3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Boceprevir and telaprevir are also contraindicated when combined with drugs that strongly induce CYP3A, which may lead to a lower exposure and reduced efficacy of hepatitis C protease inhibitors. Medications that are contraindicated with either boceprevir or telaprevir include: alfuzosin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's Wort, lovastatin, simvastatin, pimozone, sildenafil, tadalafil, triazolam, or orally-administered midazolam. In addition, carbamazepine, phenobarbital, phenytoin, and drospirenone are contraindicated with the use of boceprevir, while atorvastatin is contraindicated with the use of telaprevir.^{8,9}

Simeprevir does not induce CYP3A4 and is a substrate and mild inhibitor of intestinal CYP3A, but not hepatic CYP3A4 activity. Co-administration of simeprevir with moderate or strong inducers or inhibitors of CYP3A is not recommended as this may lead to significantly lower or higher exposure of simeprevir, respectively.¹⁰

Because the hepatitis C protease inhibitors must be used in combination with peg interferon alfa and ribavirin, the contraindications and warnings associated with those agents are also applicable to the hepatitis C protease inhibitors (Black Box Warnings associated with these agents are outlined below). Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Women of childbearing potential and men must use at least two forms of effective contraception during treatment, and for at least six months after treatment has ended. Systemic hormonal contraceptives may not be as effective in women taking hepatitis C protease inhibitors; therefore, two alternative effective methods of contraception (e.g., intrauterine devices, barrier methods) should be used in women during treatment with these agents.⁸⁻¹⁰

Anemia has been reported in patients receiving peg interferon alfa and ribavirin, and the addition of either boceprevir or telaprevir is associated with an additional decrease in hemoglobin concentrations. Complete blood counts should be monitored prior to and at least every four weeks during treatment with boceprevir or telaprevir.

For the management of anemia, ribavirin dose should be reduced. If ribavirin dose reductions are inadequate, consideration to discontinuing treatment with a boceprevir or telaprevir should be evaluated along with the ribavirin therapy.^{8,9} In contrast, no additional anemia has been observed with the addition of simeprevir to peg interferon alfa and ribavirin.¹⁰

Serious skin reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens Johnson Syndrome were reported in less than one percent of patients receiving telaprevir in combination with peg interferon alfa and ribavirin compared to none who received peg interferon alfa and ribavirin alone. Presenting signs of DRESS may include rash, fever, facial edema and evidence of internal organ involvement (e.g., hepatitis, nephritis). Eosinophilia may or may not be present. Presenting symptoms of SJS may include fever, target lesions and mucosal erosions or ulcerations (e.g., conjunctivae, lips). If serious skin reactions develop in patients receiving telaprevir, all treatment must be discontinued immediately. In addition, rash developed in 56% of patients who received telaprevir in combination with peg interferon alfa and ribavirin. Patients with mild to moderate rashes should be followed, and if the rash progresses and becomes severe or if systemic symptoms develop, telaprevir must be discontinued; however, peg interferon alfa and ribavirin may be continued.⁹

Serious acute hypersensitivity reactions (e.g., urticaria, angioedema) have been observed during combination therapy with boceprevir, peg interferon alfa and ribavirin. If such an acute reaction occurs, combination therapy should be discontinued and appropriate medical therapy immediately instituted.⁸

Rash has been reported with simeprevir in combination with peg interferon alfa and ribavirin, including severe rash requiring discontinuation of treatment. Patients with mild to moderate rashes should be followed for possible progression of rash. Treatment should be discontinued if the rash becomes severe. In addition, photosensitivity reactions (e.g., burning, erythema, exudation, blistering, and edema) have been reported with simeprevir in combination with peg interferon alfa and ribavirin, including serious reactions resulting in hospitalization. Measures to limit sun exposure are recommended. Expert consultation is advised if a decision is made to continue therapy in the setting of a photosensitivity reaction.¹⁰

As mentioned previously, according to the Food and Drug Administration approved package labeling of the hepatitis C protease inhibitors, these agents are not to be used as monotherapy and must be administered with peg interferon alfa and ribavirin.⁸⁻¹⁰

Black Boxed Warning for Incivek[®] (telaprevir)⁹

WARNING

Fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with Incivek[®] combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive Incivek[®] combination treatment after a serious skin reaction was identified. For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, Incivek[®], peg interferon alfa, and ribavirin must be discontinued immediately. Discontinuing other medications known to be associated with serious skin reactions should be considered. Patients should be promptly referred for urgent medical care.

Black Box Warning for Pegasys[®] (peg interferon alfa-2a) and Peg Intron[®] (peg interferon alfa-2b)^{29,30}

WARNING

Alfa interferons, including peg interferon alfa-2a and alfa-2b, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping peg interferon alfa-2a or alfa-2b therapy.

Use with ribavirin: ribavirin may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease.

Black Box Warnings for Copegus® (ribavirin), Rebetol® (ribavirin) and Ribasphere®/Ribasphere® RibaPak® (ribavirin)³¹⁻³³**WARNING**

Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication.

The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as six months. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for six months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the six month post treatment follow up period.

Drug Interactions**Table 7. Drug Interactions**³⁴

Generic Name	Interacting Medication or Disease	Potential Result
Hepatitis C protease inhibitors (all)	Barbiturates	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response.
Hepatitis C protease inhibitors (all)	HMG-CoA Reductase Inhibitors	HMG-CoA Reductase Inhibitors plasma concentrations may be elevated, increasing the pharmacologic effects and risk of myopathy and rhabdomyolysis. Co-administration of boceprevir or telaprevir with either lovastatin or simvastatin is contraindicated. Co-administration of atorvastatin with telaprevir is contraindicated. Atorvastatin dose should not exceed 40 mg daily when coadministered with either boceprevir or simeprevir. Rosuvastatin dose should not exceed 10 mg daily when coadministered with simeprevir.
Hepatitis C protease inhibitors (all)	Human Immunodeficiency Virus Protease Inhibitors	Hepatitis C protease inhibitor plasma concentrations may be altered by certain Human Immunodeficiency Virus Protease Inhibitors. Co-administration of simeprevir with any Human Immunodeficiency Virus Protease Inhibitor, with or without ritonavir, is not recommended. Co-administration of boceprevir or telaprevir with either darunavir/ritonavir or lopinavir/ritonavir is not recommended. Co-administration of boceprevir with atazanavir/ritonavir is not recommended. Co-administration of telaprevir with fosamprenavir/ritonavir is not recommended.
Hepatitis C protease inhibitors (all)	Hydantoins	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Hydantoin concentrations may be elevated or reduced.
Hepatitis C protease inhibitors (all)	Non-Nucleoside Reverse Transcriptase Inhibitors	Hepatitis C protease inhibitor plasma concentrations may be altered by certain Non-Nucleoside Reverse Transcriptase Inhibitors. Co-administration of boceprevir or simeprevir with efavirenz is not recommended. Telaprevir dosage should be increased to 1,125 mg every eight hours when co-administered with efavirenz. Co-administration of any Hepatitis C protease inhibitor with nevirapine is not recommended. Co-administration of simeprevir with delavirdine or etravirine is not recommended.

Generic Name	Interacting Medication or Disease	Potential Result
Hepatitis C protease inhibitors (all)	Rifamycins	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Rifamycin concentrations may be elevated by boceprevir or telaprevir, increasing the risk of adverse reactions.
Hepatitis C protease inhibitors (all)	Carbamazepine	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response.
Hepatitis C protease inhibitors (all)	Cisapride	Cisapride plasma concentrations may be elevated, increasing the pharmacologic effects and risk of cardiac arrhythmias.
Hepatitis C protease inhibitors (all)	St. John's Wort	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response
Boceprevir, telaprevir	α -1 adrenergic blockers	α -1 adrenergic blocker plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Boceprevir, telaprevir	Benzodiazepines	Plasma concentrations of certain benzodiazepines may be elevated, increasing the pharmacologic effects and risk of severe sedation and prolonged respiratory depression.
Boceprevir, telaprevir	Contraceptives, hormonal	Plasma concentrations of certain progestins may be elevated, increasing the risk of hyperkalemia. Estrogen concentrations may be reduced, increasing the risk of unintended pregnancy.
Boceprevir, telaprevir	Cyclosporine	Cyclosporine plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Boceprevir, telaprevir	Ergot derivatives	Ergot derivative plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Boceprevir, telaprevir	Phosphodiesterase Type 5 Inhibitors	Phosphodiesterase type 5 inhibitor plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions. Coadministration with a phosphodiesterase type 5 inhibitor for pulmonary hypertension is contraindicated. Coadminister phosphodiesterase type 5 inhibitors for erectile dysfunction with caution.
Boceprevir, telaprevir	Lomitapide	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity
Boceprevir, telaprevir	Pimozide	Pimozide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of life-threatening cardiac arrhythmias.
Boceprevir, telaprevir	Tacrolimus	Tacrolimus plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including QT prolongation.
Simeprevir	Antifungals	Simeprevir plasma concentrations may be increased by certain antifungals. Co-administration with systemic itraconazole, fluconazole, ketoconazole, posaconazole, and voriconazole is not recommended.
Simeprevir	Clarithromycin, erythromycin, telithromycin	Simeprevir plasma concentrations may be increased. Erythromycin plasma concentration may also be increased. Co-administration with clarithromycin, erythromycin or telithromycin is not recommended.
Simeprevir	Dexamethasone	Simeprevir plasma concentrations may be reduced by systemic dexamethasone. Co-administration with systemic dexamethasone is not recommended.

Generic Name	Interacting Medication or Disease	Potential Result
Simeprevir	Elvitegravir/cobicistat/emtricitabine/tenofovir	Simeprevir plasma concentrations may be increased by cobicistat-containing product elvitegravir/cobicistat/emtricitabine/tenofovir. Co-administration with cobicistat-containing product is not recommended.
Simeprevir	Oxcarbazepine	Simeprevir plasma concentrations may be reduced, leading to loss of virologic response.

Dosage and Administration

All three protease inhibitors are administered with food in combination with peg interferon alfa and ribavirin. Both boceprevir and telaprevir were previously indicated for three times daily administration; the prescribing information for telaprevir was recently updated recommending twice daily dosing based on comparable pharmacokinetics and safety profiles to three times daily dosing. Simeprevir is administered once-daily.⁸⁻¹⁰

In addition, the overall duration of therapy with boceprevir and telaprevir is response-guided based on hepatitis C virus (HCV) ribonucleic acid (RNA) levels at certain treatment weeks. While the overall duration of therapy with simeprevir is not response-guided, the stopping rules which allow for early discontinuation of therapy in patients with inadequate on-treatment virologic response, apply to all three protease inhibitors. In general, patients with inadequate viral response are unlikely to achieve sustained virologic response, and may develop treatment-emergent resistance substitutions. General dosing recommendations for protease inhibitors are outlined in Table 8, while the recommendations for response-guided therapy and/or stopping rules are outlined in Tables 9, 10 and 11.⁸⁻¹⁰

Boceprevir is added to peg interferon alfa and ribavirin after a four week lead-in period of peg interferon alfa and ribavirin alone (treatment weeks one through four), and is administered for either 24 or 32 weeks depending on the patient's treatment history and HCV RNA levels.⁸ Simeprevir and telaprevir are initiated with peg interferon alfa and ribavirin and administered for 12 weeks regardless of treatment history or HCV RNA levels.^{9,10}

Table 8. Dosing and Administration⁸⁻¹⁰

Generic Name	Adult Dose	Pediatric Dose	Availability
Boceprevir	<u>Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers:</u> Capsule: initial, after four weeks of peg interferon alfa and ribavirin administer 800 mg TID (every seven to nine hours) with food (a meal or light snack)	Safety and efficacy in children have not been established.	Capsule: 200 mg
Simeprevir	<u>Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers:</u> Capsule: 150 mg QD with food for 12 weeks	Safety and efficacy in children have not been established.	Capsule: 150 mg
Telaprevir	<u>Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers:</u> Tablet: 1,125 mg BID (every 10 to 14 hours) with food	Safety and efficacy in children have not been established.	Tablet: 375 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	(containing approximately 20 grams of fat) for 12 weeks		

BID=twice daily, QD=once daily, TID=three times daily

Table 9. Boceprevir Response-guided Treatment in Patients Without Cirrhosis⁸

	Assessment* (HCV RNA Results [†])		Recommendation [‡]
	At Treatment Week Eight	At Treatment Week 24	
Treatment-Naïve Patients	Undetectable	Undetectable	Complete boceprevir, peg interferon alfa and ribavirin at treatment week 28
	Detectable	Undetectable	Continue boceprevir, peg interferon alfa and ribavirin and finish through treatment week 36; then administer peg interferon alfa and ribavirin and finish through treatment week 48
Previous Partial Responders or Relapsers	Undetectable	Undetectable	Complete boceprevir, peg interferon alfa and ribavirin at treatment week 36
	Detectable	Undetectable	Continue boceprevir, peg interferon alfa and ribavirin and finish through treatment week 36; then administer peg interferon alfa and ribavirin and finish through treatment week 48
Previous Null Responders	Detectable or undetectable	Undetectable	Continue all three medications and finish through week 48.

HCV=hepatitis C virus, RNA=ribonucleic acid

*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results ≥ 100 IU/mL at treatment week 12, discontinue boceprevir, peg interferon alfa and ribavirin. If the patient has confirmed, detectable HCV-RNA at treatment week 24, then discontinue boceprevir, peg interferon alfa and ribavirin.

[†]In clinical trials, HCV RNA in plasma was measured using a Roche COBAS[®] TaqMan[®] assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 9.3 IU/mL.

[‡]Includes the four week lead in phase of peg interferon and ribavirin therapy.

Consideration should be given to treating previously untreated patients who are poorly interferon responsive (as determined at treatment week four) with four weeks peg interferon alfa and ribavirin followed by 44 weeks of boceprevir in combination with peg interferon alfa and ribavirin in order to maximize rates of sustained virologic response. Patients with cirrhosis should receive four weeks of peg interferon alfa and ribavirin followed by 44 weeks of boceprevir in combination with peg interferon alfa and ribavirin.⁸

Table 10. Simeprevir Duration of Treatment¹⁰

	Recommendations		
	Triple Therapy (Simeprevir, Peg interferon alfa and Ribavirin)*	Dual Therapy (Peg interferon alfa and Ribavirin)*	Total Treatment Duration*
Treatment-Naïve and Prior Relapse Patients Including Those with Cirrhosis	First 12 weeks	Additional 12 weeks	24 weeks
Prior Partial and Null Responder Patients Including Those with Cirrhosis	First 12 weeks	Additional 36 weeks	48 weeks

*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results ≥ 25 IU/mL at treatment week four or 12, discontinue simeprevir, peg interferon alfa and ribavirin. If the patient has HCV RNA results ≥ 25 IU/mL at treatment week 24, then discontinue peg interferon alfa and ribavirin. In clinical trials, HCV RNA in plasma was measured using a Roche COBAS[®] TaqMan[®] assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 15 IU/mL.

Table 11. Telaprevir Response-guided Treatment⁹

	Assessment* (HCV RNA Results [†])	Recommendations		
		Triple Therapy (Telaprevir, Peg interferon alfa and Ribavirin)	Dual Therapy (Peg interferon alfa and Ribavirin)	Total Treatment Duration
Treatment-Naïve and Prior Relapse Patients	Undetectable at treatment weeks four and 12	First 12 weeks	Additional 12 weeks	24 weeks
	Detectable ($\leq 1,000$ IU/mL) at treatment weeks four and/or 12	First 12 weeks	Additional 36 weeks	48 weeks
Prior Partial and Null Responder Patients	All patients	First 12 weeks	Additional 36 weeks	48 weeks

HCV=hepatitis C virus, IU=international units, RNA=ribonucleic acid

*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results $\geq 1,000$ IU/mL at treatment week four or 12, discontinue telaprevir, peg interferon alfa and ribavirin. If the patient has confirmed, detectable HCV-RNA at treatment week 24, then discontinue peg interferon alfa and ribavirin.

†In clinical trials, HCV RNA in plasma was measured using a Roche COBAS[®] TaqMan[®] assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 10 IU/mL.

Treatment-naïve patients with cirrhosis who have an undetectable HCV RNA level at treatment weeks four and 12 may benefit from an additional 36 weeks of peg interferon alfa and ribavirin (48 weeks total).⁹

Clinical Guidelines

Table 12. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases: An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection (2011)⁴	<ul style="list-style-type: none"> • The optimal therapy for hepatitis C virus (HCV) genotype 1 is the use of boceprevir or telaprevir in combination with peg interferon alfa and ribavirin. • Boceprevir and telaprevir should not be used without peg interferon alfa and weight-based ribavirin. <p><u>Treatment-naïve patients</u></p> <ul style="list-style-type: none"> • The recommended dose of boceprevir is 800 mg three times daily (every seven to nine hours) with food plus peg interferon alfa and weight-based ribavirin for 24 to 44 weeks, preceded by four weeks of lead in peg interferon alfa plus ribavirin alone. <ul style="list-style-type: none"> ○ Patients without cirrhosis treated with boceprevir, peg interferon alfa and ribavirin, whose HCV ribonucleic acid (RNA) levels at weeks eight and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (four weeks lead in of peg interferon alfa and ribavirin, followed by 24 weeks of triple therapy). ○ Triple therapy should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24. • The recommended dose of telaprevir is 750 mg three times daily (every seven to nine hours) with food (not low fat) plus peg interferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12 to 36 weeks of peg interferon alfa plus ribavirin (without telaprevir). <ul style="list-style-type: none"> ○ Patients without cirrhosis treated with telaprevir, peg interferon alfa and ribavirin, whose HCV RNA level at weeks four and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks. ○ Triple therapy should be stopped if the HCV RNA levels is $>1,000$ IU/mL at treatment weeks four or 12 and/or detectable at treatment week 24.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peg interferon alfa and ribavirin should receive therapy for a duration of 48 weeks. <p><u>Treatment-experienced patients</u></p> <ul style="list-style-type: none"> • Re-treatment with boceprevir or telaprevir, in combination with peg interferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peg interferon alfa and/or ribavirin. • Retreatment with telaprevir, in combination with peg interferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peg interferon alfa and/or weight-based ribavirin. • Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers, may be considered for partial responders, but cannot be recommended for null responders. • Patients re-treated with boceprevir plus peg interferon alfa and ribavirin who continue to have detectable HCV RNA >100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. • Patients re-treated with telaprevir plus peg interferon alfa and ribavirin who continue to have detectable HCV RNA >1,000 IU at weeks four or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. <p><u>Adverse events</u></p> <ul style="list-style-type: none"> • Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose. • Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (greater than one log increase in serum HCV RNA above nadir) is observed. • Patients who fail to have a virological response, who experience virological breakthrough or who relapse on one protease inhibitor should not be re-treated with other protease inhibitors. <p><u>Use and Interpretation of HCV RNA Results During Triple Therapy</u></p> <ul style="list-style-type: none"> • An HCV assay with a lower limit of quantification of equal to or less than 25 IU/mL and a limit of HCV RNA detection of approximately 10 to 15 IU/mL should be used for monitoring response to therapy and decision making during triple therapy. • Response-guided therapy should only be considered when no virus is detected by a sensitive assay four weeks after initiation of the HCV protease inhibitor. <p><u>IL28B testing</u></p> <ul style="list-style-type: none"> • IL28B genotype is a robust pretreatment predictor of sustained virologic response (SVR) to peg interferon alfa and ribavirin as well as to protease inhibitor triple therapy in patients with chronic HCV genotype 1. Testing may be considered when the patient or provider wish additional information on the probability of treatment response or on the probable treatment needed.
<p>Department of Veterans Affairs Hepatitis C</p>	<p><u>Recommendations in patients being considered for HCV therapy</u></p> <ul style="list-style-type: none"> • All patients with chronic HCV infection should be evaluated for HCV antiviral

Clinical Guideline	Recommendation(s)
<p>Resource Center Program and the National Hepatitis C Program Office: Update on the management and treatment of hepatitis C virus infection (2012)⁵</p>	<p>treatment.</p> <ul style="list-style-type: none"> • Patients should be counseled on their likelihood of achieving SVR, based upon individual factors such as body mass index, genotype, race, stage of fibrosis, and viral load before initiating therapy. • IL28B genotype testing can be performed before peg interferon-ribavirin therapy with or without a protease inhibitor, if the results would alter treatment decisions. <p><u>Recommendations for treatment-naïve patients with genotype 1 infection</u></p> <ul style="list-style-type: none"> • Peg interferon alfa and ribavirin, in combination with boceprevir (800 mg three times daily with food) or telaprevir (750 mg three times daily with 20 grams of fat), is the standard of care for most treatment-naïve genotype 1-infected patients. • If a telaprevir-containing regimen is used in treatment-naïve noncirrhotic patients who achieve an extended rapid virologic response (eRVR), telaprevir should be discontinued at week 12 and peg interferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable at week four, but <1,000 IU/mL and remains <1,000 IU/mL or becomes undetectable at week 12, telaprevir should be discontinued at week 12, and peg interferon-ribavirin can be continued for another 36 weeks. • If a telaprevir-containing regimen is used in treatment-naïve cirrhotics who achieve an HCV RNA that is undetectable or <1,000 IU/mL at treatment weeks four and 12, telaprevir should be discontinued at week 12, and peg interferon-ribavirin can be continued for 36 more weeks. • If a boceprevir-containing regimen is used in treatment-naïve noncirrhotics, if HCV RNA declines by $\geq 1 \log_{10}$ during the four-week lead-in, and HCV RNA is undetectable at weeks eight to 24, treatment with boceprevir-peg interferon-ribavirin for 24 weeks is sufficient. If HCV RNA is detectable at week eight, but <100 IU/mL at week 12, and negative at week 24, boceprevir-peg interferon-ribavirin should be continued until week 36, followed by peg interferon-ribavirin alone for 12 more weeks. If HCV RNA declines by $< 1 \log_{10}$ during the lead-in, boceprevir-peg interferon-ribavirin can be continued for 44 weeks. • If a boceprevir-containing regimen is used in treatment-naïve cirrhotics, 44 weeks of boceprevir-peg interferon-ribavirin is required after the four-week lead-in. <p><u>Recommendations for treatment of nonresponders and relapsers with genotype 1 infection</u></p> <ul style="list-style-type: none"> • For patients who previously failed peg interferon-ribavirin, retreatment with boceprevir or ribavirin and peg interferon-ribavirin may be considered, particularly in patients who were relapsers. • If a boceprevir-containing regimen is used for retreatment of noncirrhotic prior partial responders or relapsers, the treatment duration is 36 weeks if HCV RNA is undetectable from weeks eight to 24. If HCV RNA is detectable at week 12, but <100 IU / mL and is undetectable from weeks 24 to 36, boceprevir can be discontinued at week 36 and peg interferon-ribavirin can be continued for an additional 12 weeks. • If a boceprevir-containing regimen is used for re-treatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36. • If a boceprevir-containing regimen is used for retreatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • If a telaprevir-containing regimen is used for retreatment of prior relapsers, and HCV RNA is undetectable from weeks four and 12, telaprevir should be discontinued at week 12 and peg interferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable, but <1,000 IU/mL at week four and/or 12, telaprevir can be discontinued at week 12, and peg interferon-ribavirin can be continued for an additional 36 weeks. • If a telaprevir-containing regimen is used for re-treatment of prior partial responders or null responders, and HCV RNA is <1,000 IU/mL at weeks four and 12, telaprevir should be discontinued at week 12 and peg interferon-ribavirin should be continued for an additional 36 weeks. <p><u>Recommendations for dose modification</u></p> <ul style="list-style-type: none"> • Peg interferon alfa and ribavirin doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin or platelets. • If ribavirin is stopped for seven or more days in patients concomitantly receiving boceprevir or telaprevir, then the protease inhibitor should also be permanently discontinued. The protease inhibitors should be either continued at full dose or discontinued. • A ribavirin dose reduction should be used as initial management of HCV treatment-related anemia in a symptomatic patient with a hemoglobin <10 g/dL. Erythropoietin may be administered in patients with symptomatic anemia related to peg interferon-ribavirin therapy with or without protease inhibitors to limit anemia-related ribavirin dose reductions or dose discontinuations. • A peg interferon dose reduction should be used as initial management of HCV treatment-related neutropenia (an absolute neutrophil count of <750, or as clinically indicated). Granulocyte colony-stimulating factor should not be given as primary therapy to prevent peg interferon alfa dose reductions. <p><u>Recommendations for treatment monitoring</u></p> <ul style="list-style-type: none"> • Patients should be monitored for treatment-related adverse effects at least every two weeks early in the course of therapy, and every one to two months during treatment as clinically indicated. • Assessment of treatment adherence and screening for depression, suicidal ideation, alcohol, and illicit drug use should be performed at every visit. • Patients should be counseled about avoiding pregnancy through the use of two forms of contraception during treatment and for six months posttreatment. If a patient is receiving a boceprevir- or telaprevir-containing regimen, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners during and for at least six months after treatment. • In patients receiving telaprevir-peg interferon-ribavirin, all treatment should be stopped if any of the following occur: <ul style="list-style-type: none"> ○ HCV RNA level >1,000 IU/mL at week four or 12. ○ Detectable HCV RNA levels at week 24 or at any time point thereafter. ○ HCV RNA rebounds at any time point ($\geq 1 \log_{10}$ increase from the nadir HCV RNA). • In patients receiving boceprevir-peg interferon-ribavirin, all treatment should be stopped if any of the following occur: <ul style="list-style-type: none"> ○ HCV RNA level ≥ 100 IU/mL at week 12 with a boceprevir-containing regimen. ○ Detectable HCV RNA levels at week 24 or at any time point thereafter.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> ○ HCV RNA rebounds at any time point ($\geq 1 \log_{10}$ increase from the nadir HCV RNA). • Do not switch to the other protease inhibitor if virologic failure occurs with one protease inhibitor. <p><u>Recommendations for groups with special considerations for therapy</u></p> <ul style="list-style-type: none"> • Peg interferon alfa monotherapy may be used to treat patients with contraindications to ribavirin. • For patients who achieve RVR and have a low baseline viral load (HCV RNA <400,000 IU/mL), 24-weeks of treatment with peg interferon-ribavirin may be sufficient. • Treatment can be deferred in patients with minimal inflammation and/or minimal portal fibrosis on liver biopsy. • HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class <7), adequate neutrophils ($>1.5 \text{ k/mm}^3$), and adequate platelet counts ($>75 \text{ k/mm}^3$) should be considered for treatment with boceprevir (for 44 weeks) or telaprevir (for 12 weeks) combined with peg interferon-ribavirin at standard doses for 48 weeks. • Patients with cirrhosis continue to be at risk for hepatocellular carcinoma and should undergo routine screening regardless of viral clearance status. <p><u>Recommendations for treatment-naïve and -experienced patients with genotype 2 or 3 infection</u></p> <ul style="list-style-type: none"> • Treatment-naïve patients should be treated with peg interferon-ribavirin for 24 weeks. • For patients with low viral load (HCV RNA <600,000 IU/mL) and mild fibrosis who achieve a RVR, 12 to 18 weeks of treatment may be sufficient. • For patients with genotype 3 infection and a high HCV RNA (>600,000 IU/mL), steatosis or advanced fibrosis, treatment beyond 24 weeks may improve response. • Retreatment duration is 48 weeks. <p><u>Recommendations in patients with genotype 4 infection</u></p> <ul style="list-style-type: none"> • Appropriate candidates with HCV genotype 4 infections should be treated with peg interferon alfa-2a 180 µg per week or peg interferon alfa-2b 1.5 µg / kg per week, plus ribavirin up to 1,400 mg per day for 48 weeks. <p><u>Recommendations in patients with decompensated cirrhosis</u></p> <ul style="list-style-type: none"> • Liver transplantation is the treatment of choice in patients with decompensated cirrhosis. • Antiviral therapy is contraindicated in most patients with decompensated cirrhosis. • Interferon-based therapy in combination with ribavirin can be considered for patients awaiting liver transplantation if they have a Child-Pugh score <7 and a Model for End-Stage Liver Disease score ≤ 18. • If beginning antiviral therapy, the interferon dose should be reduced and growth factors may be used to for treatment-associated cytopenias. <p><u>Recommendations in patients following solid organ transplantation</u></p> <ul style="list-style-type: none"> • Interferon-based antiviral therapy is contraindicated in patients who have received a heart, lung or kidney transplant. • In patients with biopsy-proven chronic HCV disease following liver transplantation, peg interferon-ribavirin for 48 weeks may be considered. • Monitor antiviral therapy in post-liver transplant patients on antiviral therapy

Clinical Guideline	Recommendation(s)
	<p>and discontinue if rejection is documented. Pre-emptive antiviral therapy early post-transplantation in patients without histological recurrence should be avoided.</p> <p><u>Recommendations in patients with renal disease</u></p> <ul style="list-style-type: none"> • Considered modified doses of antiviral therapy with interferon (standard or pegylated). • Antiviral therapy for HCV treatment is not recommended in patients following renal transplant; however, it may be considered if patients develop fibrosing cholestatic hepatitis. <p><u>Recommendations in patients with comorbid conditions</u></p> <ul style="list-style-type: none"> • Antiviral therapy is not recommended in patients with a limited life expectancy. In addition, peg interferon-ribavirin, treatment should be avoided in comorbid conditions that may be exacerbated by treatment. <p><u>Recommendations for patients on methadone</u></p> <ul style="list-style-type: none"> • Antiviral therapy should be offered to patients enrolled in a methadone maintenance program who meet criteria for therapy. Coordinated HCV treatment between providers and substance abuse specialists should occur. <p><u>Recommendations in patients with ongoing alcohol use</u></p> <ul style="list-style-type: none"> • Encourage patients to decrease alcohol consumption or to abstain, and refer for behavioral intervention to reduce alcohol use. Antiviral therapy may be used in patients who are otherwise appropriate candidates, regardless of prior alcohol use. Alcohol reduces adherence and treatment response. <p><u>Recommendations in obese patients and those with hepatic steatosis</u></p> <ul style="list-style-type: none"> • Patients with a body mass index >30 should be considered for antiviral treatment. Control comorbid conditions prior to initiation of antiviral therapy. <p><u>Recommendations in patients with human immunodeficiency virus (HIV)/HCV coinfection</u></p> <ul style="list-style-type: none"> • Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy. Treatment should consist of peg interferon-ribavirin at doses similar to those with HCV for a duration of 48 weeks. <p><u>Recommendations in patients with acute HCV infection</u></p> <ul style="list-style-type: none"> • Observe patients for eight to 20 weeks from time of initial exposure to monitor for spontaneous resolution of infection. • In patients who fail to resolve infection spontaneously, treatment with peg interferon alfa, with or without ribavirin for 24 to 48 weeks should be used, based on genotype and HCV RNA response during therapy.
<p>American Association for the Study of Liver Diseases: Diagnosis, Management, and Treatment of Hepatitis C: An Update (2009)²</p>	<ul style="list-style-type: none"> • Treatment decisions should be individualized based on severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions and the patient's readiness for treatment. • Optimal therapy for chronic HCV infection is peg interferon alfa in combination with ribavirin. • In genotypes 1 and 4, treatment with peg interferon alfa and ribavirin for 48 weeks is recommended. In patients who do not achieve an early virological response (early virologic response; ≥ 2 log reduction in HCV RNA at 12 weeks), treatment may be discontinued. Patients who do not achieve a

Clinical Guideline	Recommendation(s)
	<p>complete early virologic response (undetectable HCV RNA at 12 weeks) should be re-tested at week 24, and if HCV RNA remains positive, treatment should be discontinued. Finally, for patients who have delayed virus clearance (HCV RNA test becomes negative between 12 and 24 weeks); consideration should be given to extending therapy to 72 weeks.</p> <ul style="list-style-type: none"> • In genotypes 2 or 3, treatment with peg interferon alfa and ribavirin for 24 weeks is recommended. Patients who receive treatment for 24 weeks and who have a negative HCV RNA measurement, should be retested for HCV RNA 24 weeks later to evaluate for a SVR. Regardless of genotype, patients with HCV-related cirrhosis who achieve a SVR should be monitored at six to 12 month intervals for hepatocellular carcinoma development. • The same criteria for evaluating which patients should receive treatment can be used to determine which children, age two to 17 years of age, who are infected with HCV should receive treatment. • Children should be treated with the combination of peg interferon alfa 2b, 60 µg/m² weekly, and ribavirin 15 mg/kg daily for 48 weeks.
<p>European Association for the Study of the Liver: Management of Hepatitis C Virus Infection (2013)³</p>	<p><u>Goals and endpoints of HCV therapy</u></p> <ul style="list-style-type: none"> • The goal of therapy is to eradicate HCV infection. • The endpoint of therapy is SVR, defined by undetectable HCV RNA 24 weeks after the end of therapy; SVR usually equates to cure of infection in more than 99% of patients. • Undetectable HCV RNA at 12 weeks after the end of therapy (SVR 12) has been accepted in the US and Europe given concordance with SVR 24 is 99%; however, this concordance needs to be further validated in ongoing clinical trials. <p><u>Indications for treatment</u></p> <ul style="list-style-type: none"> • All treatment-naïve patients with compensated disease due to HCV should be considered for therapy. • Treatment should be scheduled, not deferred, for patients with significant fibrosis (F3 to F4). • In patients with less severe disease, indication for and timing of therapy can be individualized. <p><u>First line treatment of chronic hepatitis C genotype 1</u></p> <ul style="list-style-type: none"> • Triple therapy with boceprevir or telaprevir added to peg interferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotype 1. There is no head-to-head comparison to allow recommendation of boceprevir or telaprevir as preferred therapy. • Patients with cirrhosis should never receive abbreviated treatment with boceprevir or telaprevir regimens. • Selected patients with high likelihood of SVR to peg interferon alfa and ribavirin or with contraindications to boceprevir or telaprevir can be treated with dual therapy. • When lead-in is used to identify patients with peg interferon alfa sensitive infection, the possibility of continuation of dual therapy should have been discussed with the patient prior to initiation of treatment. • Both peg interferon alfa-2a (180 µg/week) and peg interferon alfa-2b (1.5 µg/kg/week) can be used in dual or triple therapy. • Ribavirin should be dosed following the peg interferon alfa label for triple therapy. • Ribavirin should be administered at a weight-based dose of 15 mg/kg/day in dual therapy

Clinical Guideline	Recommendation(s)
	<p><u>First line treatment of chronic hepatitis C genotypes 2, 3, 4, 5, and 6</u></p> <ul style="list-style-type: none"> The combination of peg interferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotypes 2, 3, 4, 5, and 6. Ribavirin should be administered at a weight-based dose of 15 mg/kg/day for genotypes 4, 5 and 6, and at a flat dose of 800 mg/day for genotypes 2 and 3. Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at a dose of 15 mg/kg/day. <p><u>Treatment monitoring</u></p> <ul style="list-style-type: none"> A real-time polymerase chain reaction-based assay with a lower limit of detection of <15 IU/mL should be used to monitor triple therapy. During triple therapy in HCV genotype 1 patients, HCV RNA measurements should be performed at weeks four, eight, 12, 24, and end of treatment when administering boceprevir, and at weeks four, 12, 24, and end of treatment when administering telaprevir. During dual therapy in any HCV genotype, HCV RNA levels should be assessed at baseline, weeks four, 12, 24 and end of treatment. The end-of-treatment virological response and the SVR at 12 or 24 weeks after the end of treatment must be assessed. Whether the baseline HCV RNA level is low or high may be a useful criterion to guide treatment decisions during dual therapy. The safest threshold level for discriminating low and high baseline HCV RNA is 400,000 IU/mL. Dual therapy for all HCV genotypes should be stopped at week 12 if the HCV RNA decrease is <2 log₁₀ IU/mL and at week 24 if HCV RNA is still detectable. Triple therapy with boceprevir should be stopped if HCV RNA is >100 IU/mL at treatment week 12 or if HCV RNA is detectable at treatment week 24. Triple therapy with telaprevir should be stopped if HCV RNA is >1,000 IU/mL at weeks four or 12 of therapy. Dual therapy duration should be tailored to the on-treatment virological response at weeks four and 12. The likelihood of SVR is directly proportional to the rapidity of HCV RNA disappearance. For patients receiving dual therapy who achieve an RVR and who have low baseline viral titre (<400,000 IU/mL), treatment for 24 weeks (genotype 1) or 16 weeks (genotype 2 or 3) can be considered. If negative predictors of response (i.e., advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic steatosis) are present, published evidence for equal efficacy of shortened treatment is lacking. Patients receiving dual therapy with genotypes 2 or 3, and with any adverse predictor of SVR, and who achieve an early virological response or a delayed virological response without an RVR, can be treated for 48 weeks. Genotype 1 patients receiving dual therapy who demonstrate a delayed virological response can be treated for 72 weeks, provided that their HCV RNA is undetectable at week 24. <p><u>Treatment dose reductions and stopping rules</u></p> <ul style="list-style-type: none"> The peg interferon alfa dose should be reduced if the absolute neutrophil count falls below 750/mm³, or the platelet count falls below 50,000/mm³. Peg interferon alfa should be stopped if the neutrophil count falls below 500/mm³ or the platelet count falls below 25,000/mm³ or if severe unmanageable depression develops. If neutrophil or platelet counts rise, treatment can be restarted, but at a reduced peg interferon alfa dose.

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> • If hemoglobin <10 g/dL occurs, the dose of ribavirin should be adjusted downward by 200 mg at a time, and ribavirin should be stopped if hemoglobin falls below 8.5 g/dL. • Treatment should be stopped in case of a severe hepatitis flare or severe sepsis. • Boceprevir or telaprevir doses should not be reduced during therapy due to the risk of the development of antiviral resistance. If boceprevir or telaprevir have been stopped, they should never be reintroduced in the same course of treatment. <p><u>Measures to improve treatment success rates</u></p> <ul style="list-style-type: none"> • Full adherence to all antiviral drugs should be the aim in order to optimize SVR rates and to reduce the risk of emergence of specific drug resistance. • Body weight adversely influences the response to peg interferon alfa and ribavirin; therefore, a reduction of body weight in overweight patients prior to therapy may increase the likelihood of SVR. • Insulin resistance is associated with treatment failure for dual therapy; however, insulin sensitizers have no proven efficacy in improving SVR rates in these patients. • Counseling on abstaining from alcohol during antiviral therapy should be provided. • In dual therapy, recombinant erythropoietin can be administered when the hemoglobin level falls <10 g/dL in order to reduce the need for ribavirin dose reduction. • In patients receiving boceprevir or telaprevir-based triple therapy, ribavirin dose reduction should be the initial response to significant anemia. • There is no evidence that neutropenia during peg interferon alfa and ribavirin therapy is associated with more frequent infection episodes, or that the use of granulocyte colony stimulating factor reduces the rate of infections and/or improves SVR rates. • Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy. Patients who develop depression during therapy should be treated with antidepressants. Preventative antidepressant therapy in selected patients may reduce the incidence of this condition during treatment, without any impact on SVR. <p><u>Post treatment follow up of patients who achieve an SVR</u></p> <ul style="list-style-type: none"> • Noncirrhotic patients with SVR should be retested for alanine transaminase and HCV RNA at 48 weeks post-treatment, and then discharged if alanine transaminase is normal and HCV RNA is negative. • Cirrhotic patients with SVR should undergo surveillance for hepatocellular carcinoma every six months by means of ultrasound. • If present, portal hypertension and esophageal varices should be managed, though index variceal bleed is seldom observed in low-risk patients after the achievement of SVR. • Patients with ongoing drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection. • Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on people who inject drugs with ongoing risk behavior. <p><u>Retreatment of nonsustained virological responders to peg interferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> • Patients infected with HCV genotype 1 who failed to eradicate HCV in prior

Clinical Guideline	Recommendation(s)
	<p>therapy with peg interferon alfa and ribavirin should be considered for retreatment with the triple combination of peg interferon alfa, ribavirin and a protease inhibitor.</p> <ul style="list-style-type: none"> • The previous response to interferon-based therapy is an important predictor of success of triple therapy. If the pattern of prior response to dual therapy is not clearly documented, the patient should not be treated with abbreviated response-guided therapy. • Patients with cirrhosis and prior null responders have a lower chance of cure and should not be treated with response-guided therapy with either boceprevir or telaprevir. • Patients infected with HCV genotypes other than 1 and who failed on prior therapy with non-pegylated interferon alfa, with or without ribavirin, can be re-treated with pegylated interferon alfa and ribavirin. <p><u>Treatment of patients with severe liver disease</u></p> <ul style="list-style-type: none"> • Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short to midterm complications. • Monitoring and management of side effects, especially those linked to portal hypertension, low platelet count, and low serum albumin should be done particularly carefully. Growth factors may be useful in this group. • Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. • In patients awaiting liver transplantation, antiviral therapy, when feasible, prevents graft reinfection if an SVR is achieved. • Antiviral therapy may be started while awaiting liver transplantation, with the goal of achieving SVR or HCV RNA negativity before transplantation. • In patients with Child-Pugh B cirrhosis, antiviral therapy is offered on an individual basis in experienced centers, preferentially in patients with predictors of good response. • Patients with Child-Pugh C cirrhosis should not be treated with the current interferon alfa-based antiviral regimens due to a high risk of life-threatening complications. • Treatment can be started at low doses of peg interferon alfa and ribavirin, following a low accelerated dose regimen or at full doses. In the latter case, dose reductions and treatment interruptions are required in >50% of cases. • Patients with post-transplant recurrence of HCV infection should initiate therapy once chronic hepatitis is established and histologically proven. Significant fibrosis or portal hypertension one year after transplantation predicts rapid disease progression and graft loss and indicates urgent antiviral treatment. • For patients with HCV genotype 1, protease inhibitor-based therapy can be used, but frequent monitoring and dose adjustment of tacrolimus and cyclosporine are required. • Graft rejection is rare but may occur during peg interferon alfa treatment. A liver biopsy should be performed whenever liver tests worsen on antiviral therapy. <p><u>Treatment of special groups</u></p> <ul style="list-style-type: none"> • Indications for HCV treatment in patients with human immunodeficiency virus (HIV) coinfection are identical to those in patients with HCV mono-infection. The same peg interferon alfa regimen should be used in HIV coinfecting patients. Longer treatment duration may be considered for patients with genotype 2 and 3 who exhibit slow early viral kinetics. • Patients coinfecting with HIV and HCV genotype 1 should be considered for

Clinical Guideline	Recommendation(s)
	<p>telaprevir or boceprevir triple therapy regimen, but special care should be taken to minimize or avoid potential drug-drug interactions.</p> <ul style="list-style-type: none"> • HIV patients with a diagnosis of acute HCV infection should be treated with peg interferon and ribavirin, with duration dependent on viral kinetics independent of HCV genotype. • Patients coinfecting with hepatitis B should be treated with telaprevir or boceprevir triple therapy regimen, following the same rules as monoinfected patients. • If hepatitis B virus replicates at significant levels before, during or after HCV clearance, concurrent hepatitis B virus nucleoside/nucleotide analogue therapy is indicated. • Patients on hemodialysis, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. • Antiviral treatment should comprise peg interferon alfa at an appropriately reduced dose. • Ribavirin can be used at very low doses, but with caution. • Boceprevir or telaprevir can be used with caution in patients with impaired creatinine clearance, and dose adjustment is probably unnecessary. • Patients with HCV and end stage renal disease scheduled for kidney transplantation should undergo antiviral therapy prior to transplantation due to the increased risk of acute transplant rejection. • Interferon alfa-based antiviral treatment is associated with a significant risk of renal graft rejection, and it should be avoided unless there is a powerful indication for antiviral treatment (e.g., aggressive cholestatic hepatitis). • Regular alcohol consumption should be strongly discouraged. • Treatment of patients with active illicit drug abuse has to be individualized. • Patients with hemoglobinopathies can be treated with combination therapy but need careful monitoring. <p><u>Follow up of untreated patients and of patients with treatment failure</u></p> <ul style="list-style-type: none"> • Untreated patients with chronic hepatitis C and those who failed prior treatment should be followed regularly. • Non-invasive methods for staging fibrosis are best suited for follow-up assessment at intervals. • Hepatocellular carcinoma screening must be continued indefinitely in patients with cirrhosis. <p><u>Treatment of acute hepatitis C</u></p> <ul style="list-style-type: none"> • Peg interferon alfa monotherapy for 24 weeks is recommended in patients with acute hepatitis C and achieves SVR in >90% of patients. • Patients failing to respond to monotherapy should be retreated according to the standard of care for chronic hepatitis C.
Centers for Disease Control and Prevention: Hepatitis ABC Fact Sheet (2012) ⁷	<p><u>Hepatitis C</u></p> <ul style="list-style-type: none"> • For acute hepatitis C, antivirals and supportive treatments are used. • Regular monitoring for signs of liver disease progression is required and some patients are treated with antiviral drugs.
American Gastroenterological Association: Medical Position Statement on the Management of Hepatitis C (2006) ⁶	<ul style="list-style-type: none"> • The treatment of choice is peg interferon plus ribavirin. • Patients with genotypes 1 and 4 require 48 weeks of therapy with peg interferon and high daily doses of ribavirin (1,000 to 1,200 mg, depending on weight). • Patients with genotypes 2 and 3 can be treated for only 24 weeks with peg interferon and 800 mg of ribavirin daily, with the following exceptions: <ul style="list-style-type: none"> • A longer duration of therapy may be considered on an individual

Clinical Guideline	Recommendation(s)
	<p>patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy.</p> <ul style="list-style-type: none"> • Twelve weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week four. • Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks.

Conclusions

Boceprevir (Victrelis[®]), simeprevir (Olysio[®]), and telaprevir (Incivek[®]) are Food and Drug Administration (FDA)-approved for the treatment of adults with chronic hepatitis C genotype 1 infection with compensated liver disease (including cirrhosis). Hepatitis C protease inhibitors inhibit the replication of hepatitis C virus (HCV) host cells by binding to the nonstructural 3/4A protease of HCV genotype 1a and 1b. All three agents are FDA-approved for use in treatment-naïve patients as well as those who have been previously treated with interferon-based treatment, including prior null responders, partial responders and relapsers. Protease inhibitors must be administered in combination with peg interferon alfa and ribavirin. Because of this, warnings and precautions that are associated with these agents are applicable to protease inhibitor combination treatment.⁸⁻¹⁰

Boceprevir is added to standard therapy (peg interferon alfa and ribavirin) after a four week lead-in period with standard therapy alone. It is administered three times daily for either 24, 32 or 44 weeks based on a patient's treatment history and HCV ribonucleic acid (RNA) levels.⁸ Simeprevir and telaprevir can be initiated with standard therapy and are administered once daily and two times daily, respectively, for 12 weeks, regardless of treatment history or HCV RNA levels.^{9,10} Boceprevir and telaprevir are associated with an increased risk of anemia when administered with standard therapy.^{8,9} In addition, telaprevir is associated with the development of rash, which can be serious in nature.⁹ Prior to initiating therapy with simeprevir, patients with HCV genotype 1a should be screened for the presence of NS3 Q80K polymorphism that is associated with substantially reduced efficacy of simeprevir combination therapy. Alternative therapy should be considered for patients with HCV genotype 1a infection with the Q80K polymorphism.¹⁰

The pivotal clinical trials demonstrate that use of the hepatitis C protease inhibitors, in combination with peg interferon alfa and ribavirin, results in significantly higher sustained virologic response (SVR) rates among adult patients with chronic hepatitis C genotype 1 infection compared to standard therapy alone. In select patients with satisfactory early virologic responses, the total treatment duration may be shortened (i.e., response-guided treatment).^{13-15,17,18,23-25} Specifically, clinical trial data demonstrates, and FDA-approved dosing states, that if a patient has an undetectable HCV RNA level at treatment weeks four and 12 with a telaprevir-containing regimen, 24 weeks of total treatment is effective in achieving a SVR.^{9,14,15,18} A patient with an undetectable HCV RNA level at treatment weeks eight and 24 with a boceprevir-containing regimen requires 28 or 36 weeks of total treatment depending on their previous treatment history.^{9,13,17} The total duration of treatment with simeprevir-containing regimen is either 24 weeks in treatment-naïve and prior relapser patients or 48 weeks in prior partial and null responder patients.^{10,23-26} Of note, standard treatment futility rules apply to any triple therapy regimen used for the treatment of chronic hepatitis C genotype 1 infection. Futility should be assessed at treatment weeks four, 12 and 24 with simeprevir and telaprevir-containing regimens, and at treatment weeks 12 and 24 with boceprevir-containing regimens.⁸⁻¹⁰

Combination treatment with peg interferon alfa and ribavirin has been the standard of care for the treatment of chronic hepatitis C.³⁻⁶ The hepatitis C protease inhibitors are recommended, along with standard therapy, for the treatment of chronic hepatitis C genotype 1 infection.^{3,4} To date, no head-to-head trials between the commercially available hepatitis C protease inhibitors have been published to directly compare their efficacy. Treatment guidelines do not give preference to one specific peg interferon alfa or ribavirin product over another.³⁻⁷ Furthermore, no one protease inhibitor is preferred over another and current recommendations for their use are in line with FDA-approved indications and dosing.²⁻¹⁰ Treatment guidelines were published prior to the availability of simeprevir and sofosbuvir and do not address the place in therapy of these two agents.²⁻⁷

References

1. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010 Dec 17;59(RR-12):1-110.
2. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, Management and treatment of hepatitis C; An Update. 2009. *Hepatology* 2009; 49(4):1-40.
3. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol*. 2013 Dec 4.
4. American Association for the Study of Liver Diseases (AASLD). 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 [guideline on the internet]. Geneva, Switzerland: American Association for the Study of Liver Diseases; 2013 [cited 2014 Jan 17]. Available from: <http://www.aasld.org/practiceguidelines/Documents/AASLDUpdateTreatmentGenotype1HCV11113.pdf>.
5. Yee HS, Chang MF, Pocha C, Lim J, Ross D, Morgan TR, et al. Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. *Am J Gastroenterol*. 2012 May;107(5):669-89.
6. Dienstag JL, McHutchison JG. American Gastroenterological Association Medical position statement on the management of hepatitis C. *Gastroenterology*. 2006;130(1):225-30.
7. Centers for Disease Control and Prevention. The ABCs of Hepatitis Fact Sheet [guideline on the Internet]. Atlanta (GA): CDC 2012 Aug [cited 2014 Jan 16]. Available at: <http://www.cdc.gov/hepatitis/resources/professionals/pdfs/abctable.pdf>.
8. Victrelis[®] [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2013 Sep.
9. Incivek[®] [package insert]. Cambridge (MA): Vertex Pharmaceuticals Incorporated; 2013 Oct.
10. Olysio[®] [package insert]. Titusville (NJ): Janssen Therapeutics; 2013 Nov.
11. Sovaldi[®] [package insert on the internet]. Foster City (CA): Gilead Sciences, Inc.; 2013 Dec.
12. Micromedex[®] Healthcare Series [intranet database]. Version 5.1. Greenwood Village, Colo: Thomson Healthcare. Cited 2013 Dec]. Available from: <http://www.thomsonhc.com/>.
13. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011 Mar 31;364:1195-206.
14. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011;364:2405-16.
15. Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med*. 2011;365:1014-24.
16. Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H, Hayashi N. Telaprevir with peg interferon and ribavirin for treatment-naïve patients chronically infected with HCV of genotype 1 in Japan. *J Hepatol*. 2012 Jan;56(1):78-84.
17. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011 Mar 31;364:1207-17.
18. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med*. 2011;364:2417-28.
19. Hayashi N, Okanoue T, Tsubouchi H, Toyota J, Chayama K, Kumada H. Efficacy and safety of telaprevir, a new protease inhibitor, for difficult-to-treat patients with genotype 1 chronic hepatitis C. *J Viral Hepat*. 2012 Feb;19(2):e134-42.
20. Flamm SL, Lawitz E, Jacobson I, Bourlière M, Hezode C, Vierling JM, et al. Boceprevir with peg interferon alfa-2a-ribavirin is effective for previously treated chronic hepatitis C genotype 1 infection. *Clin Gastroenterol Hepatol*. 2013 Jan;11(1):81-87.
21. Kwo PY, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peg interferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomized, multicenter phase 2 trial. *Lancet*. 2010;376:705-16.
22. Pawlotsky JM. The results of phase III clinical trials with telaprevir and boceprevir presented at the Liver Meeting 2010: a new standard of care for hepatitis C virus genotype 1 infection, but with issues still pending. *Gastroenterology*. 2011;140:746-60.
23. Jacobson I, Dore GJ, Foster GR, Fried M, Radu M, Rafalskiy V, et al. Simeprevir (TMC435) with peg interferon/ribavirin for chronic HCV genotype-1 infection in treatment-naïve patients: results from QUEST-

- 1, a phase III trial. Poster presented at Digestive Disease Week (DDW); Orlando, FL; May 18-21, 2013. Poster 1674582.
24. Poordad F, Manns M, Marcellin P, Affonso de Araujo ES, Buti M, et al. Simeprevir with peg interferon- α 2a or - α 2b and ribavirin in treatment-naïve HCV genotype-1 patients: QUEST-2, a randomized phase III trial. Data presented at Digestive Disease Week (DDW); Orlando, FL; May 18-21, 2013.
25. Lawitz E, Forns X, Zeuzem S, Gane E, Bronowicki JP, Andreone P et al. Simeprevir with peg interferon/ribavirin for treatment of chronic HCV genotype 1 infection in patients who relapsed after previous interferon-based therapy: results from PROMISE, a phase III trial. Data presented at Digestive Disease Week (DDW); Orlando, FL; May 18-21, 2013.
26. Zeuzem S, Berg T, Gane E, Ferenci P, Foster GR, Fried MW, et al. Simeprevir Increases Rate of Sustained Virologic Response Among Treatment-Experienced Patients with HCV Genotype-1 Infection: a Phase IIb Trial [published online ahead of print]. *Gastroenterology*. 2013 Oct 31.
27. Jacobson IM, Ghalib RH, Rodriguez-Torres M, Younossi ZM, Corregidor A, Sulkowski MS et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study. American Association for the Study of Liver Diseases (AASLD 2013). Washington. November 1-5, 2013. Abstract 1840610.
28. Results from the COSMOS study with Simeprevir and Sofosbuvir in cirrhotic and non-cirrhotic HCV genotype 1 patients presented at AASLD [press release on the Internet]. Stockholm, Sweden: Medivir AB; 2013 Nov 4 [cited 2013 Dec 12]. Available from: <http://www.medivir.se/v5/en/uptodate/pressrelease.cfm?releaseid=4E7105B904E97096&year=2013>.
29. Pegasys® [package insert]. South San Francisco (CA): Genentech USA, Inc.; 2013 Jul.
30. Peg Intron® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2013 Nov.
31. Copegus® [package insert]. South San Francisco (CA): Genentech, Inc.; 2013 Feb.
32. Rebetol® [package insert]. Whitehouse Station (NJ): Schering-Plough Corporation; 2013 Nov.
33. Ribasphere® [package insert]. Warrendale (PA): Kadmon Pharmaceuticals, LLC; 2012 Feb.
34. Drug Facts and Comparisons [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Dec]. Available from: <http://online.factsandcomparisons.com>.