

## Retreatment of Persons in Whom Prior Therapy Failed

This section provides guidance on the retreatment of persons with chronic HCV infection in whom prior therapy failed. The level of the evidence available to inform the best regimen for each patient and the strength of the recommendation vary, and are rated accordingly (see [Methods Table 2](#)). In addition, specific recommendations are given when treatment differs for a particular group (eg, those infected with different viral genotypes). Recommended regimens are those that are favored for most patients in that group, based on optimal efficacy, favorable tolerability and toxicity profiles, complexity, and treatment duration.

Alternative regimens are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data. In certain situations, an alternative regimen may be optimal for a specific patient.

Specific considerations for [pediatric patients](#) and persons with [HIV/HCV coinfection](#), [decompensated cirrhosis](#) (moderate or severe hepatic impairment; [Child-Turcotte-Pugh \[CTP\] class B or C](#)), HCV infection [post liver transplantation](#), and [severe renal impairment](#), end-stage renal disease (ESRD), or HCV infection [post kidney transplantation](#) are addressed in other sections of the guidance.

Recommended and alternative regimens are listed in order of level of evidence. When several regimens are at the same recommendation level, they are listed in alphabetical order. Regimen choice should be determined based on patient-specific data, including drug interactions. Patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients require careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen (See [Monitoring section](#)).

### Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals (DAAs) are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration of treatment is unclear, expert consultation should be sought.

The following pages include guidance for management of treatment-experienced patients.

- [Genotype 1](#)
- [Genotype 2](#)
- [Genotype 3](#)
- [Genotype 4](#)
- [Genotype 5 or 6](#)
- [Glecaprevir/Pibrentasvir Treatment Failures \(All Genotypes\)](#)
- [Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failure \(All Genotypes\)](#)

**Last update:** November 6, 2019

## Treatment-Experienced Genotype 1

Multiple highly potent, DAA combination regimens are recommended for patients with genotype 1 infection. There are differences in the recommended regimens based on viral subtype, the presence or absence of baseline NS5A resistance-associated substitutions (RASs), the presence or absence of compensated cirrhosis, and the type of prior failed regimen(s). Genotype 1 infection that cannot be subtyped should be treated as genotype 1a.

Approximately 10% to 15% of genotype 1 patients without prior exposure to NS5A inhibitors have detectable NS5A RASs prior to treatment. The clinical impact of NS5A RASs varies across regimens and baseline patient characteristics. In patients with genotype 1a, the presence of baseline NS5A RASs that cause a large reduction in the activity of NS5A inhibitors (>5 fold) adversely impacts response to some NS5A inhibitor-containing regimens ([Zeuzem, 2017](#)); ([Jacobson, 2015b](#)). These RASs are found by population sequencing in roughly 5% to 10% of patients; relevant RASs vary by DAA regimen. Given that baseline NS5A RASs are one of the strongest pretreatment predictors of therapeutic outcome with certain regimens in genotype 1a patients, testing for these RASs prior to deciding on a therapeutic course is recommended in selected situations ([Zeuzem, 2015c](#)). For further guidance, please see the [Resistance Primer](#) section.

Compared to interferon-based therapy, DAAs are associated with a higher rate of drug interactions with concomitant medications. With combinations of DAAs in the various treatment regimens, attention to drug-drug interactions is that much more important (see [Drug Interactions table](#)). The product prescribing information and other resources (eg, <http://www.hep-druginteractions.org>) should be consulted regularly to ensure safety when prescribing DAA regimens. Important interactions with commonly used medications (eg, antacids, lipid-lowering drugs, anti-epileptics, antiretrovirals, etc) exist for all regimens discussed.

The following pages include guidance for management of treatment-experienced patients with genotype 1.

- [Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis](#)
- [Peginterferon/Ribavirin-Experienced, Genotype 1a Patients With Compensated Cirrhosis](#)
- [Peginterferon/Ribavirin-Experienced, Genotype 1b Patients Without Cirrhosis](#)
- [Peginterferon/Ribavirin-Experienced, Genotype 1b Patients With Compensated Cirrhosis](#)
- [NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients Without Cirrhosis](#)
- [NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients With Compensated Cirrhosis](#)
- [Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients Without Cirrhosis](#)
- [Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients With Compensated Cirrhosis](#)
- [NS5A Inhibitor DAA-Experienced \(Excluding Glecaprevir/Pibrentasvir Failures\), Genotype 1 Patients, With or Without Compensated Cirrhosis](#)
- [Glecaprevir/Pibrentasvir Treatment Failures \(All Genotypes\)](#)
- [Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failure \(All Genotypes\)](#)

**Last update:** November 6, 2019

## Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

## Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING <sup>i</sup>
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs <sup>a</sup> for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup>	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

<sup>a</sup> Includes genotype 1a RASs at amino acid positions 28, 30, 31, or 93 known to confer [antiviral resistance to elbasvir](#). Baseline testing for these RASs is recommended for patients receiving elbasvir/grazoprevir-based regimens.

<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

### Elbasvir/Grazoprevir

The phase 3 C-EDGE TE trial evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) in patients with a prior peginterferon/ribavirin treatment failure. Patients were randomized to elbasvir/grazoprevir for 12 weeks or 16 weeks, with or without ribavirin. Genotype 1 patients treated for 12 weeks without ribavirin had an overall SVR<sub>12</sub> of 93.8% (90/96), which was nearly identical to the rate seen in those treated for 12 weeks with ribavirin (94.4%, 84/89) ([Kwo, 2017](#)). SVR rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a patients with baseline NS5A RASs (>5 fold), only 52% (11/21) achieved SVR<sub>12</sub> due to a higher relapse rate ([Kwo, 2015](#)).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR<sub>12</sub> in treatment-experienced, genotype 1a patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) ([Zeuzem, 2017](#)). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR<sub>12</sub>, compared to 96% (52/54) among those without these baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen ([Jacobson, 2015b](#)).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended for genotype 1a patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. A prospective real-world study confirmed high response rates based on this approach ([Braun, 2019](#)). Given the need for ribavirin and the prolonged duration of therapy in the presence of key NS5A RASs as well as multiple

preferred regimens, elbasvir/grazoprevir plus ribavirin for 16 weeks has been removed as an alternative regimen. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

### Glecaprevir/Pibrentasvir

The phase 3 ENDURANCE-1 trial enrolled 703 treatment-naïve or -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 1 and no cirrhosis. Participants were randomized to 8 weeks or 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills ([Zeuzem, 2016](#)). Of those enrolled, 43% had genotype 1a, 85% had fibrosis stage F0 or F1, and 38% were treatment experienced. Ninety-nine percent of the treatment-experienced patients had previously received interferon-based therapy and 1% had received sofosbuvir-based treatment. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority. A single patient experienced on-treatment virologic failure (genotype 1a, day 29). There were no documented relapses in either study arm. This regimen was well tolerated with rare adverse events leading to discontinuation (0.1%); no significant laboratory abnormalities were noted.

### Ledipasvir/Sofosbuvir

The daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) has been evaluated in patients without cirrhosis and a history of treatment failure with peginterferon/ribavirin, with or without HCV protease inhibitors (telaprevir or boceprevir). In the ION-2 study, patients who had not responded to prior peginterferon/ribavirin therapy were treated with ledipasvir/sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In the population without cirrhosis, the overall SVR12 rate was 98%. Specifically, in patients without cirrhosis and a history of peginterferon/ribavirin failure, 94% (33/35) achieved SVR12 after 12 weeks of ledipasvir/sofosbuvir treatment, and 100% (38/38) achieved SVR12 in the ledipasvir/sofosbuvir plus ribavirin study arm ([Afdhal, 2014b](#)). This regimen was well tolerated in all groups with no serious adverse events reported for the 12-week regimen, with or without ribavirin.

### Sofosbuvir/Velpatasvir



The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naïve or -experienced patients with genotype 1, 2, 4, 5, or 6 who were treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks ([Feld, 2015](#)). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a and 97% (31/32) in those with genotype 1b. Among patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. The regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) vs the placebo group (77%).

**Last update:** November 6, 2019

## Peginterferon/Ribavirin-Experienced, Genotype 1a Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

## Peginterferon/Ribavirin-Experienced, Genotype 1a Patients With Compensated Cirrhosis<sup>a</sup>

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs <sup>b</sup> for elbasvir	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>c</sup>	12 weeks	I, B
ALTERNATIVE	DURATION	RATING 
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	I, A

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

<sup>b</sup> Includes genotype 1a RASs at amino acid positions 28, 30, 31, or 93 known to confer [antiviral resistance to elbasvir](#). Baseline testing for these RASs is recommended for patients receiving elbasvir/grazoprevir-based regimens.

<sup>c</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

## Recommended Regimens

### Elbasvir/Grazoprevir

The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) was evaluated in patients with a history of failed peginterferon/ribavirin therapy in the C-EDGE TE study. In this phase 3 trial, patients were randomized to 12 weeks or 16 weeks of elbasvir/grazoprevir, with or without ribavirin. Genotype 1 patients treated for 12 weeks without ribavirin had an overall SVR12 of 93.8% (90/96), which was nearly identical to the response rate in patients treated for 12 weeks with added ribavirin (94.4%, 84/89) ([Kwo, 2017](#)). Response rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96). A subset analysis of patients with compensated cirrhosis revealed similar response rates to the population without cirrhosis when treated with elbasvir/grazoprevir without ribavirin for 12 weeks (SVR12 with cirrhosis 95% [19/20]; SVR12 without cirrhosis 94.9% [37/39]).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a patients with baseline NS5A RASs (>5 fold), only 52.4% (11/21) achieved SVR due to a higher relapse rate ([Kwo, 2015](#)).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR12 rate in treatment-experienced, genotype 1a patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) ([Zeuzem, 2017](#)). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR12 compared to 96% (52/54) among those without baseline RASs.



Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen ([Jacobson, 2015b](#)).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [ $<75$  kg] to 1200 mg [ $\geq 75$  kg]) is recommended to decrease relapse risk. A prospective real-world study confirmed high response rates based on this approach ([Braun, 2019](#)). Given the need for ribavirin and the prolonged duration of therapy in the presence of key NS5A RASs as well as multiple preferred regimens, elbasvir/grazoprevir plus ribavirin for 16 weeks has been removed as an alternative regimen. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

## Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive and -experienced patients with genotype 1, 2, 4, 5, or 6 treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks ([Feld, 2015](#)). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1 treatment-experienced patients was 99% (109/110), with 100% (78/78) among participants with genotype 1a and 97% (31/32) in those with genotype 1b. Among patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR12; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR12. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. This regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) versus the placebo group (77%).

## Glecaprevir/Pibrentasvir

The EXPEDITION-1 trial investigated use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks in 146 patients with compensated cirrhosis infected with genotype 1, 2, 4, 5, or 6. Twenty-five percent (36/146) of enrolled patients were non-DAA treatment experienced. SVR12 was 98.9% (89/90) among genotype 1 patients. The single treatment failure occurred in a patient with genotype 1a who relapsed at post-treatment week 8 ([Forns, 2017](#)). Ninety-one percent of patients (133/146) had a Child-Pugh score of 5 and 9% (13/146) had a Child-Pugh score of 6. Twenty percent of patients had a platelet count  $<100 \times 10^9/L$  and all but 1 participant had a normal albumin level. In this patient population with compensated cirrhosis, the regimen was safe and well tolerated. There were 11 serious adverse events; none were DAA-related and no adverse events led to discontinuation of the study drugs. Glecaprevir/pibrentasvir is a safe and highly efficacious 12-week regimen in patients with well-compensated cirrhosis.

## Alternative Regimen

### Ledipasvir/Sofosbuvir + Ribavirin

The double-blind, placebo-controlled, phase 2 SIRIUS trial enrolled genotype 1 patients with compensated cirrhosis who did not achieve SVR12 with peginterferon/ribavirin plus telaprevir or boceprevir. Participants were randomized to either 12 weeks of placebo followed by 12 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin, or ledipasvir/sofosbuvir plus placebo for 24 weeks. The SVR12 rates were similar in the study arms: 96% (74/77) in the group that received ledipasvir/sofosbuvir plus ribavirin for 12 weeks (3 relapses), and 97% (75/77) in the group that received ledipasvir/sofosbuvir for 24 weeks (2 relapses) ([Bourliere, 2015](#)).

These findings are further supported by a post hoc analysis of treatment-naive or -experienced, genotype 1 patients with compensated cirrhosis who were treated with ledipasvir/sofosbuvir in phase 2 and phase 3 studies (including the SIRIUS trial). In this analysis, ledipasvir/sofosbuvir for 12 weeks was inferior to ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Safety and tolerability were similar in the groups and, apart from anemia, reported adverse events did not differ


substantially between patients treated with or without ribavirin ([Reddy, 2015](#)). Due to the need for ribavirin, this regimen is recommended as an alternative for genotype 1 patients with compensated cirrhosis and a history of peginterferon/ribavirin treatment failure.

Baseline NS5A RASs adversely impact response to ledipasvir/sofosbuvir therapy. The magnitude of impact varies based on several factors, including virus (genotype subtype, specific RAS); regimen (companion drugs, use of ribavirin); and patient factors (treatment experience, presence of cirrhosis). In an analysis of more than 350 genotype 1 treatment-experienced patients with cirrhosis, the presence of baseline ledipasvir RASs (defined as RASs resulting in a >2.5-fold shift in ledipasvir EC<sub>50</sub>) detected at a 1% level resulted in a lower SVR12 compared to those without baseline RASs ([Zeuzem, 2017](#)). The SVR12 rates were 89% with RASs versus 96% in the absence of RASs with a 12-week course of ledipasvir/sofosbuvir plus ribavirin, and 87% versus 100%, respectively, with a 24-week course of ledipasvir/sofosbuvir without ribavirin. The impact of baseline RASs is likely greater in a genotype 1a only population.

Given the vulnerable nature of this population, baseline NS5A resistance testing should be considered for genotype 1a treatment-experienced patients with compensated cirrhosis prior to use of ledipasvir/sofosbuvir. If ledipasvir-associated RASs are detected, a different regimen should be used to optimize treatment response.

**Last update:** November 6, 2019

## Peginterferon/Ribavirin-Experienced, Genotype 1b Patients Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:		
Peginterferon/Ribavirin-Experienced, Genotype 1b Patients Without Cirrhosis		
RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>a</sup>	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

<sup>a</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

### Elbasvir/Grazoprevir

The phase 3 C-EDGE TE trial evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) in patients with a prior peginterferon/ribavirin treatment failure. Patients were randomized to elbasvir/grazoprevir for 12 weeks or 16 weeks, with or without ribavirin. Genotype 1 patients treated for 12 weeks without ribavirin had an overall SVR12 of 93.8% (90/96), which was nearly identical to the response rate in patients treated for 12 weeks with added ribavirin (94.4%, 84/89) ([Kwo, 2017](#)). SVR rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a patients with baseline NS5A RASs (>5 fold), only 52% (11/21) achieved SVR due to a higher relapse rate ([Kwo, 2015](#)).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR in treatment-experienced genotype 1a patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) ([Zeuzem, 2017](#)). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR, compared to 96% (52/54) among those without these baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen ([Jacobson, 2015b](#)).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended for genotype 1a patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [ $<75$  kg] to 1200 mg [ $\geq 75$  kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

## Glecaprevir/Pibrentasvir

The phase 3 ENDURANCE-1 trial enrolled 703 treatment-naïve or -experienced patients (interferon or peginterferon  $\pm$  ribavirin, or sofosbuvir plus ribavirin  $\pm$  peginterferon) with genotype 1 and no cirrhosis. Participants were randomized to 8 weeks or 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills ([Zeuzem, 2016](#)). Of those enrolled, 43% had genotype 1a, 85% had fibrosis stage F0 or F1, and 38% were treatment experienced. Ninety-nine percent of the treatment-experienced patients had previously received interferon-based therapy and 1% had received sofosbuvir-based treatment. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority. A single patient experienced on-treatment virologic failure (genotype 1a, day 29). There were no documented relapses in either study arm. This regimen was well tolerated with rare adverse events leading to discontinuation (0.1%); no significant laboratory abnormalities were noted.

## Ledipasvir/Sofosbuvir

The daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) has been evaluated in patients without cirrhosis and a history of treatment failure with peginterferon/ribavirin, with or without HCV protease inhibitors (telaprevir or boceprevir). In the ION-2 study, patients who had not responded to prior peginterferon/ribavirin therapy were treated with ledipasvir/sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In the population without cirrhosis, the overall SVR was 98%. Specifically, in patients without cirrhosis and a history of peginterferon/ribavirin failure, 94% (33/35) achieved SVR12 after 12 weeks of ledipasvir/sofosbuvir treatment, and 100% (38/38) achieved SVR in the ledipasvir/sofosbuvir plus ribavirin study arm ([Afdhal, 2014b](#)). This regimen was well tolerated in all groups with no serious adverse events reported for the 12-week regimen, with or without ribavirin.

## Sofosbuvir/Velpatasvir





The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naïve or -experienced patients with genotype 1, 2, 4, 5, or 6 who were treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks ([Feld, 2015](#)). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1 treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a and 97% (31/32) in those with genotype 1b. Among patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR12; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR12. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. The regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) vs the placebo group (77%).

**Last update:** November 6, 2019

## Peginterferon/Ribavirin-Experienced, Genotype 1b Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

### Peginterferon/Ribavirin-Experienced, Genotype 1b Patients With Compensated Cirrhosis<sup>a</sup>

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup>	12 weeks	I, B
ALTERNATIVE	DURATION	RATING 
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	I, A

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

## Recommended Regimens

### Elbasvir/Grazoprevir

The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) was evaluated in patients with a history of

failed peginterferon/ribavirin therapy in the C-EDGE TE study. In this phase 3 trial, patients were randomized to 12 weeks or 16 weeks of elbasvir/grazoprevir, with or without ribavirin. Genotype 1 patients treated for 12 weeks without ribavirin had an overall SVR12 rate of 93.8% (90/96), which was nearly identical to the response rate in patients treated for 12 weeks with added ribavirin (94.4%, 84/89) ([Kwo, 2017](#)). Response rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96). A subset analysis of patients with compensated cirrhosis revealed similar response rates to the population without cirrhosis when treated with elbasvir/grazoprevir without ribavirin for 12 weeks (SVR12 with cirrhosis 95% [19/20]; SVR12 without cirrhosis 94.9% [37/39]).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a-infected patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a-infected patients with baseline NS5A RASs (>5 fold), only 52.4% (11/21) achieved SVR due to a higher relapse rate ([Kwo, 2015](#)).

## Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive and -experienced patients with genotype 1, 2, 4, 5, or 6 treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks ([Feld, 2015](#)). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1 treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a and 97% (31/32) in those with genotype 1b. Among patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR12; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR12. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. This regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) versus the placebo group (77%).

## Glecaprevir/Pibrentasvir

The EXPEDITION-1 trial investigated use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks in 146 patients with compensated cirrhosis infected with genotype 1, 2, 4, 5, or 6. Twenty-five percent (36/146) of enrolled patients were non-DAA treatment experienced. SVR12 was 98.9% (89/90) among genotype 1 patients. The single treatment failure occurred in a patient with genotype 1a who relapsed at post-treatment week 8 ([Forns, 2017](#)). Ninety-one percent of patients (133/146) had a Child-Pugh score of 5 and 9% (13/146) had a Child-Pugh score of 6. Twenty percent of patients had a platelet count <100 x 10<sup>9</sup>/L and all but 1 participant had a normal albumin level. In this patient population with compensated cirrhosis, the regimen was safe and well tolerated. There were 11 serious adverse events; none were DAA-related and no adverse events led to discontinuation of the study drugs. Glecaprevir/pibrentasvir is a safe and highly efficacious 12-week regimen in patients with well-compensated cirrhosis.

## Alternative Regimen

### Ledipasvir/Sofosbuvir + Ribavirin

The double-blind, placebo-controlled, phase 2 SIRIUS trial enrolled genotype 1 patients with compensated cirrhosis who did not achieve SVR with peginterferon/ribavirin plus telaprevir or boceprevir. Participants were randomized to either 12 weeks of placebo followed by 12 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin, or ledipasvir/sofosbuvir plus placebo for 24 weeks. The SVR rates were similar in the study arms: 96% (74/77) in the group that received ledipasvir/sofosbuvir plus ribavirin for 12 weeks (3 relapses), and 97% (75/77) in the group that received ledipasvir/sofosbuvir for 24 weeks (2 relapses) ([Bourliere, 2015](#)).

These findings are further supported by a post hoc analysis of treatment-naive or -experienced, genotype 1 patients with compensated cirrhosis who were treated with ledipasvir/sofosbuvir in phase 2 and phase 3 studies (including the SIRIUS

trial). In this analysis, ledipasvir/sofosbuvir for 12 weeks was inferior to ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Safety and tolerability were similar in the groups and, apart from anemia, reported adverse events did not differ substantially between patients treated with or without ribavirin ([Reddy, 2015](#)). Due to the need for ribavirin, this regimen is recommended as an alternative for genotype 1 patients with compensated cirrhosis and a history of peginterferon/ribavirin treatment failure.

**Last update:** November 6, 2019

## NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:		
<b>NS3 Protease Inhibitor (Telaprevir, Boceprevir, or Simeprevir) + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients Without Cirrhosis</b>		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>a</sup>	12 weeks	IIa, B
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for all genotype 1b patients, and genotype 1a patients without baseline NS5A RAS <sup>b</sup> for elbasvir	12 weeks	IIa, B
<hr/>		
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for genotype 1a patients with baseline NS5A RAS <sup>b</sup> for elbasvir	16 weeks	IIa, B
<p><sup>a</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.</p> <p><sup>b</sup> Includes genotype 1a RASs at amino acid positions 28, 30, 31, or 93 known to confer <a href="#">antiviral resistance to elbasvir</a>. Baseline testing for these RASs is recommended for patients receiving elbasvir/grazoprevir-based regimens.</p>		

## Recommended Regimens

### Ledipasvir/Sofosbuvir

The ION-2 trial evaluated the safety and efficacy of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in genotype 1 patients in whom prior treatment with an HCV protease inhibitor (telaprevir or boceprevir) plus peginterferon/ribavirin failed ([Afdhal, 2014b](#)). SVR12 rates with the 12-week and 24-week ledipasvir/sofosbuvir regimens were 94% and 98%, respectively. Relapse rates were numerically higher with the 12-week regimen versus the 24-week regimen. The presence of cirrhosis and/or baseline NS5A RASs were the major reasons for the higher relapse rate in the 12-week study arm. Thus, genotype 1 patients without cirrhosis in whom a prior regimen of peginterferon/ribavirin plus an HCV protease inhibitor failed can receive a 12-week course of ledipasvir/sofosbuvir.

### Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naïve or -experienced patients with genotype 1, 2, 4, 5, or 6 treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks ([Feld, 2015](#)). In this study, 100% (48/48) of participants who previously experienced treatment failure with a protease inhibitor plus peginterferon/ribavirin achieved SVR12 ([Feld, 2015](#)). These data are supported by a similarly high SVR12 rate seen in a preceding phase 2, open-label trial wherein 100% (27/27) of patients with the same type of treatment failure history achieved SVR12 with 12 weeks of sofosbuvir/velpatasvir therapy ([Pianko, 2015](#)).

### Glecaprevir/Pibrentasvir

In parts 1 and 2 of the MAGELLAN-1 trial, 42 genotype 1 patients had been previously treated with either an NS5A inhibitor or a protease inhibitor. Twenty-four percent of these patients had cirrhosis. Among those previously treated with protease inhibitor-based therapy (includes simeprevir, boceprevir, or telaprevir without NS5A inhibitor exposure) who were retreated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks, 92% (23/25) achieved SVR12. Simeprevir plus sofosbuvir failures were included. Of the 2 patients who did not achieve SVR12, neither experienced virologic failure ([Poordad, 2017](#)); ([Poordad, 2017b](#)).

## Alternative Regimen

### Elbasvir/Grazoprevir + Ribavirin

Grazoprevir is a next-generation HCV NS3/4A protease inhibitor that retains activity in vitro against many common protease inhibitor resistant substitutions ([Summa, 2012](#)); ([Howe, 2014](#)). Elbasvir is an HCV NS5A inhibitor. The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with expanded weight-based ribavirin (800 mg to 1400 mg) was evaluated in an open-label, phase 2 study of 79 patients who experienced prior treatment failure with interferon-based therapy plus a protease inhibitor ([Forns, 2015a](#)). Most enrolled participants had a prior treatment failure with peginterferon/ribavirin plus either boceprevir (35%, n=28) or telaprevir (54%, n=43). Importantly, 83% of enrolled patients had experienced virologic failure with their prior protease inhibitor-containing regimen and 44% had detectable NS3 RASs to early-generation protease inhibitors at study entry. SVR12 was attained in 96% of patients, including in 93% (28/30) of genotype 1a patients and 94% (32/34) in those with cirrhosis. Baseline NS3 RASs did not appear to have a large impact on treatment response with an SVR12 of 91% (31/34). Presence of NS5A or dual NS3/NS5A substitutions was associated with lower SVR12 rates of 75% and 66%, respectively. But with only 3 failures in the entire study, firm conclusions cannot be drawn.

Consistent with recommendations for other populations, a 12-week course of elbasvir/grazoprevir is a recommended regimen for patients with genotype 1a infection and no baseline NS5A RASs. Extension of therapy to 16 weeks plus weight-based ribavirin is an alternative treatment option for genotype 1a patients with baseline NS5A RASs resulting in a >5-fold shift in elbasvir potency.

Last update: November 6, 2019

## NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

### NS3 Protease Inhibitor (Telaprevir, Boceprevir, or Simeprevir) + Peginterferon/Ribavirin Treatment-Experienced, Genotype 1 Patients With Compensated Cirrhosis<sup>a</sup>

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup>	12 weeks	IIa, B
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for all genotype 1b patients, and genotype 1a patients without baseline NS5A RASs <sup>c</sup> for elbasvir	12 weeks	IIa, B
<hr/>		
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for genotype 1a patients with baseline NS5A RASs <sup>c</sup> for elbasvir	16 weeks	IIa, B

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

<sup>c</sup> Includes genotype 1a RASs at amino acid position 28, 30, 31, or 93 known to confer [antiviral resistance to elbasvir](#). Baseline testing for these RASs is recommended for patients receiving elbasvir/grazoprevir-based regimens.

## Recommended Regimens



## Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naïve or -experienced patients with genotype 1, 2, 4, 5, or 6 treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks ([Feld, 2015](#)). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1 treatment-experienced patients was 99.1% (109/110), with 100% (78/78) in patients with genotype 1a and 96.9% (31/32) among those with genotype 1b. In this study, 100% (48/48) of participants who previously experienced treatment failure with a protease inhibitor plus peginterferon/ribavirin achieved SVR12 ([Feld, 2015](#)). These data are supported by similarly high SVR12 rate seen in a preceding phase 2, open-label trial wherein 100% (27/27) of patients with the same type of treatment failure history achieved SVR12 with 12 weeks of sofosbuvir/velpatasvir therapy ([Pianko, 2015](#)).

## Glecaprevir/Pibrentasvir

In parts 1 and 2 of the MAGELLAN-1 trial, 42 genotype 1 patients had been previously treated with either an NS5A inhibitor or a protease inhibitor. Twenty-four percent of these patients had cirrhosis. Among those previously treated with NS3/4A protease inhibitor-based therapy (includes simeprevir, boceprevir, or telaprevir without NS5A inhibitor exposure) who were retreated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks, 92% (23/25) achieved SVR12. Simeprevir plus sofosbuvir failures were included. Of the 2 patients who did not achieve SVR, neither experienced virologic failure ([Poordad, 2017](#)); ([Poordad, 2017b](#)).

## Alternative Regimens

### Ledipasvir/Sofosbuvir + Ribavirin

The ION-2 trial evaluated the safety and efficacy of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in genotype 1 patients in whom prior treatment with an HCV protease inhibitor (telaprevir or boceprevir) plus peginterferon/ribavirin failed ([Afdhal, 2014b](#)). SVR12 with 12 weeks of therapy was 94%. Relapse rates were numerically higher in the 12-week treatment arms than in the 24-week arms. The pretreatment presence of cirrhosis and/or NS5A RASs were the major reasons for the higher relapse rate in the 12-week arm. Thus, genotype 1 patients without cirrhosis in whom a prior regimen of peginterferon/ribavirin plus an HCV protease inhibitor failed should receive ledipasvir/sofosbuvir plus weight-based ribavirin for 12 weeks to optimize treatment response ([Bourliere, 2015](#)). Due to the need for ribavirin, this is recommended as an alternative regimen.

### Elbasvir/Grazoprevir + Ribavirin

Grazoprevir is a next-generation HCV NS3/4A protease inhibitor that retains activity in vitro against many common protease inhibitor RASs ([Summa, 2012](#)); ([Howe, 2014](#)). Elbasvir is an HCV NS5A inhibitor. The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with expanded weight-based ribavirin (800 mg to 1400 mg) was evaluated in an open-label, phase 2 study of 79 patients who experienced a prior treatment failure with interferon-based therapy plus a protease inhibitor ([Forns, 2015a](#)). Most enrolled participants had a prior treatment failure with peginterferon/ribavirin plus either boceprevir (35%, n=28) or telaprevir (54%, n=43). Importantly, 83% of enrolled patients had experienced virologic failure with their prior protease inhibitor-containing regimen and 44% had detectable NS3 RASs to early-generation protease inhibitors at study entry. SVR12 was attained in 96% of patients, including 93% (28/30) of genotype 1a patients and 94% (32/34) of those with cirrhosis. Baseline NS3 RASs did not appear to have a large impact on treatment response with an SVR12 of 91% (31/34). Presence of NS5A or dual NS3/NS5A substitutions was associated with lower SVR12 rates of 75% and 66%, respectively. But with only 3 failures in the entire study, firm conclusions cannot be drawn.



Consistent with recommendations for other populations, extension of therapy to 16 weeks with ribavirin is recommended for patients with baseline NS5A RASs resulting in a >5-fold shift in elbasvir potency. Due to the need for ribavirin, both the 12-week and 16-week course of therapy are recommended as alternative regimens.

Last update: November 6, 2019

## Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

### Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) for genotype 1a patients	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>a</sup> , regardless of subtype	12 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for genotype 1b patients	12 weeks	IIa, B
ALTERNATIVE	DURATION	RATING 
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin, except in simeprevir failures	12 weeks	IIa, B

<sup>a</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

## Recommended Regimens

### Sofosbuvir/Velpatasvir/Voxilaprevir

The phase 3, open-label, randomized clinical trial POLARIS-4 compared a 12-week course of daily fixed-dose sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) to 12 weeks of sofosbuvir/velpatasvir in non-NS5A inhibitor DAA-experienced patients ([Bourliere, 2017](#)). Overall, 69% of patients were previously exposed to sofosbuvir plus ribavirin ± peginterferon, and 11% were exposed to sofosbuvir plus simeprevir. Cirrhosis was common, 46% in both study arms. SVR12 rates for patients with genotype 1 were 97% (76/78) for sofosbuvir/velpatasvir/voxilaprevir and 90% (60/66) for sofosbuvir/velpatasvir. Only sofosbuvir/velpatasvir/voxilaprevir met the prespecified efficacy (SVR12) threshold of 85%. There was 1 relapse in the sofosbuvir/velpatasvir/voxilaprevir arm compared to 15 virologic failures (14 relapses, 1 virologic breakthrough) in the sofosbuvir/velpatasvir group. The single patient who experienced relapse in the

sofosbuvir/velpatasvir/voxilaprevir arm did not have treatment-emergent RASs; 9 of the patients with relapse in the sofosbuvir/velpatasvir arm developed NS5A treatment-emergent RASs. This study supports sofosbuvir/velpatasvir/voxilaprevir as a recommended regimen for the treatment of patients with a history of treatment failure using a non-NS5A inhibitor sofosbuvir-containing DAA regimen.

## Glecaprevir/Pibrentasvir

There are limited data to guide recommendations for the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for patients with genotype 1a or 1b and a prior treatment failure with a sofosbuvir-containing DAA regimen. In the phase 3, open-label ENDURANCE-1 study, 351 and 352 patients received 8 weeks or 12 weeks of glecaprevir/pibrentasvir, respectively ([Zeuzem, 2016](#)). All patients had genotype 1 and were noncirrhotic; 38% of patients in each study arm were treatment experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). However, only 1 patient in the 8-week arm and 2 patients in the 12-week arm had a history of treatment failure with a sofosbuvir-containing regimen.

In the EXPEDITION-1 study, 146 patients with genotype 1, 2, 4, 5, or 6 and compensated cirrhosis were treated with 12 weeks of glecaprevir/pibrentasvir. Twenty-five of these patients were treatment experienced; only 11 had a previous treatment failure with a sofosbuvir-containing regimen ([Forns, 2017](#)). None of these patients had a prior simeprevir plus sofosbuvir regimen failure. However, 12 weeks of glecaprevir/pibrentasvir was evaluated in prior NS3/4A treatment failures in the MAGELLAN-1 trial, which included patients with prior simeprevir plus sofosbuvir treatment failure ([Poordad, 2017](#)); ([Poordad, 2017b](#)).

With the limited clinical trial experience with glecaprevir/pibrentasvir in patients with a history of sofosbuvir-containing regimen treatment failure coming primarily from a 12-week duration of therapy, we recommend 12 weeks of therapy in this patient population until there are further clinical trial or real-world data to support a shorter treatment duration.

## Sofosbuvir/Velpatasvir

As described in the discussion of sofosbuvir/velpatasvir/voxilaprevir, the POLARIS-4 trial included a 12-week arm of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in non-NS5A inhibitor-DAA experienced patients ([Bourliere, 2017](#)). While only sofosbuvir/velpatasvir/voxilaprevir met the overall prespecified efficacy (SVR12) threshold of 85%, this was primarily driven by treatment failure in patients with genotype 1a or 3. Forty-four patients with genotype 1a, 22 with genotype 1b, 33 with genotype 2, and 52 with genotype 3 were included in the sofosbuvir/velpatasvir arm. Overall, there were 15 virologic failures (14 relapses); 5 were in genotype 1a patients and 8 were in those with genotype 3. One genotype 1b patient and a single genotype 2 patient also experienced treatment failure. Although this study was not powered to assess differences in efficacy by genotype/subtype, the SVR12 rates in genotype 1b patients were 95% and 96% for sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, respectively. There were fewer genotype 1b patients who experienced a previous treatment failure specifically with a non-NS5A inhibitor sofosbuvir-containing regimen (n=12), and no virologic failures.

## Alternative Regimen

### Ledipasvir/Sofosbuvir + Ribavirin


Retreatment with the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in patients with genotype 1, with or without cirrhosis, in whom a sofosbuvir-containing (excluding simeprevir) regimen failed was evaluated in 2 small pilot studies utilizing ledipasvir/sofosbuvir for 12 weeks. Among patients with a prior treatment failure with 24 weeks of sofosbuvir plus ribavirin, a high SVR was achieved when patients were retreated with 12 weeks of ledipasvir/sofosbuvir ([Osinusi, 2014](#)). Ledipasvir/sofosbuvir plus ribavirin has also been evaluated in patients in whom prior treatment with sofosbuvir plus peginterferon/ribavirin or sofosbuvir and ribavirin failed. In a study of 51 patients, retreatment with ledipasvir/sofosbuvir plus ribavirin for 12 weeks led to SVR12 in 100% of 50 patients with genotype 1. One virologic failure was observed in a patient determined to have genotype 3 prior to retreatment ([Wyles, 2015b](#)).

Last update: November 6, 2019

## Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients With Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

### Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients With Compensated Cirrhosis<sup>a</sup>

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for genotype 1a patients	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup> , regardless of subtype	12 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for genotype 1b patients	12 weeks	IIa, B

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

### Sofosbuvir/Velpatasvir/Voxilaprevir

The phase 3, open-label, randomized clinical trial POLARIS-4 compared a 12-week course of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) to 12 weeks of sofosbuvir/velpatasvir in non-NS5A inhibitor DAA-experienced patients ([Bourliere, 2017](#)). Overall, 69% of patients were previously exposed to sofosbuvir plus ribavirin ± peginterferon, and 11% were exposed to sofosbuvir plus simeprevir. Cirrhosis was common, 46% in both study arms. SVR12 rates for patients with genotype 1 were 97% (76/78) for sofosbuvir/velpatasvir/voxilaprevir and 90% (60/66) for sofosbuvir/velpatasvir. Only sofosbuvir/velpatasvir/voxilaprevir met the prespecified efficacy (SVR12) threshold of 85%. The vast majority of patients had experienced prior treatment failure with a sofosbuvir plus simeprevir regimen. Overall, there was 1 relapse in the sofosbuvir/velpatasvir/voxilaprevir arm compared to 15 virologic failures (14 relapses, 1 virologic breakthrough) in the sofosbuvir/velpatasvir group. The single patient who experienced relapse in the sofosbuvir/velpatasvir/voxilaprevir arm did not have treatment-emergent RASs; 9 of the patients with relapse in the sofosbuvir/velpatasvir arm developed NS5A treatment-emergent RASs. This study supports sofosbuvir/velpatasvir/voxilaprevir as a recommended regimen for the treatment of patients with a history of treatment failure with a sofosbuvir-containing DAA regimen, regardless of the presence of cirrhosis.

## Glecaprevir/Pibrentasvir

In the EXPEDITION-1 study, 146 patients with genotype 1, 2, 4, 5, or 6 and compensated cirrhosis were treated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks ([Forns, 2017](#)). Of these patients, 25 patients were previously treated with interferon or peginterferon ± ribavirin and 11 were previously treated with sofosbuvir and ribavirin ± peginterferon. Overall, 99% (145/146) of patients achieved SVR12. The single patient who did not respond to therapy had genotype 1a and relapsed at post-treatment week 8. None of the patients enrolled in the EXPEDITION-1 trial were previously treated with simeprevir plus sofosbuvir. However, 12 weeks of glecaprevir/pibrentasvir was evaluated in patients with NS3/4A treatment failure in the MAGELLAN-1 trial, which included simeprevir plus sofosbuvir treatment failures ([Poordad, 2017](#)); ([Poordad, 2017b](#)).

## Sofosbuvir/Velpatasvir

As described in the discussion of sofosbuvir/velpatasvir/voxilaprevir, the POLARIS-4 trial included a 12-week arm of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in non-NS5A inhibitor DAA-experienced patients ([Bourliere, 2017](#)). While only sofosbuvir/velpatasvir/voxilaprevir met the overall prespecified efficacy (SVR12) threshold of 85%, this was primarily driven by treatment failure in patients with genotype 1a or 3. Forty-four patients with genotype 1a, 22 with genotype 1b, 33 with genotype 2, and 52 with genotype 3 were included in the sofosbuvir/velpatasvir arm. Overall, there were 15 virologic failures (14 relapses); 5 were in genotype 1a patients and 8 were in those with genotype, and most of these patients had cirrhosis. One genotype 1b patient and a single genotype 2 patient also experienced treatment failure. Although this study was not powered to assess differences in efficacy by genotype/subtype, the SVR12 rates in genotype 1b patients were 95% and 96% for sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, respectively. There were fewer genotype 1b patients who had specifically experienced a prior non-NS5A inhibitor sofosbuvir-containing regimen failure (n=12), and no virologic failures.

**Last update:** November 6, 2019

## NS5A Inhibitor DAA-Experienced (Excluding Glecaprevir/Pibrentasvir Failures), Genotype 1 Patients, With or Without Compensated Cirrhosis

(For [glecaprevir/pibrentasvir treatment failures](#), please see that topic.)



Recommended and alternative regimens listed by evidence level and alphabetically for:

## NS5A Inhibitor DAA-Experienced (Excluding Glecaprevir/Pibrentasvir Failures), Genotype 1 Patients, With or Without Compensated Cirrhosis<sup>a</sup>



RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup> except NS3/4 protease inhibitor inclusive DAA combination regimens	16 weeks	Ila, B

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.  
<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

## Recommended Regimen

### Sofosbuvir/Velpatasvir/Voxilaprevir

The placebo-controlled, phase 3 POLARIS-1 trial evaluated a 12-week course of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) in patients with a prior NS5A inhibitor-containing DAA regimen. The majority (61%) experienced a failure with a combination regimen of an NS5B inhibitor plus an NS5A inhibitor, such as sofosbuvir/ledipasvir ([Bourliere, 2017](#)). The overall SVR12 was 97% (146/150) in genotype 1 patients. SVR12 rates were 96% (97/101) for participants with genotype 1a and 100% (45/45) for those with genotype 1b. A single genotype 1 patient experienced relapse; this individual had subtype 1a and cirrhosis. Baseline RASs and the presence of cirrhosis were not significant predictors of virologic failure with genotype 1. Serious adverse events were similar in the placebo and treatment arms; only 1 patient discontinued therapy due to an adverse event. Headache, diarrhea, and nausea were more common in those patients receiving sofosbuvir/velpatasvir/voxilaprevir compared to placebo.

## Alternative Regimen

### Glecaprevir/Pibrentasvir

In parts 1 and 2 of the MAGELLAN-1 trial, 42 genotype 1 patients had previously been treated with either an NS5A inhibitor or an NS3/4A protease inhibitor ([Poordad, 2017](#)); ([Poordad, 2017b](#)). Twenty-four percent of these patients had cirrhosis; 79% had genotype 1a. Patients who were previously treated with an NS5A inhibitor (ledipasvir or daclatasvir) and not concomitantly treated with a NS3/4A protease inhibitor were retreated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 16 weeks. Among these patients, 94% (16/17) achieved SVR12. The single patient who did not respond to therapy had an on-treatment virologic failure. Due to the 16-week duration of therapy and limited supporting data, this is recommended as an alternative regimen.

Last update: November 6, 2019

## Treatment-Experienced Genotype 2

The following pages include guidance for management of treatment-experienced patients with genotype 2.


- [Peginterferon/Ribavirin-Experienced, Genotype 2 Patients Without Cirrhosis](#)
- [Peginterferon/Ribavirin-Experienced, Genotype 2 Patients With Compensated Cirrhosis](#)
- [DAA-Experienced \(Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures\), Genotype 2 Patients, With or Without Compensated Cirrhosis](#)
- [Glecaprevir/Pibrentasvir Treatment Failures \(All Genotypes\)](#)
- [Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failure \(All Genotypes\)](#)

Last update: November 6, 2019

## Peginterferon/Ribavirin-Experienced, Genotype 2 Patients Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

### Peginterferon/Ribavirin-Experienced, Genotype 2 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>a</sup>	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

<sup>a</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

### Glecaprevir/Pibrentasvir

The SURVEYOR-II, part 4 trial was a single-arm study of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 8 weeks in noncirrhotic

patients with genotype 2, 4, 5, or 6 who were treatment-naïve or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) ([Asselah, 2018b](#)). One hundred forty-five genotype 2 patients were enrolled with a 98% SVR12. Two patients experienced relapse; both were treatment experienced.

## Sofosbuvir/Velpatasvir

In the randomized, open-label ASTRAL-2 study, genotype 2 patients were treated with 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) or sofosbuvir plus ribavirin ([Foster, 2015a](#)). Of the 266 participants, a minority (15%) had a history of previous peginterferon/ribavirin treatment failure and a similar proportion (14%) had compensated cirrhosis. Overall, the combination of sofosbuvir/velpatasvir yielded a statistically significant superior SVR12 rate of 99% vs 94% for sofosbuvir plus ribavirin. The only treatment failure in the sofosbuvir/velpatasvir arm was a patient who withdrew from the study after a single day due to side effects (anxiety). In contrast, there were 6 virologic failures in the sofosbuvir plus ribavirin arm. Fatigue and anemia were more commonly reported in patients receiving sofosbuvir plus ribavirin.


The phase 3 POLARIS-2 study randomized patients to 8 weeks of the fixed-dose combination of sofosbuvir/velpatasvir/voxilaprevir versus 12 weeks of sofosbuvir/velpatasvir. Fifty-three genotype 2 patients were in the sofosbuvir/velpatasvir arm and all achieved SVR (100%, 53/53) ([Jacobson, 2017](#)). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2, including those with a past peginterferon/ribavirin treatment failure and patients with compensated cirrhosis.

**Last update:** November 6, 2019

## Peginterferon/Ribavirin-Experienced, Genotype 2 Patients With Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

### Peginterferon/Ribavirin-Experienced, Genotype 2 Patients With Compensated Cirrhosis<sup>a</sup>

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup>	12 weeks	I, B

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

## Sofosbuvir/Velpatasvir

In the randomized, open-label ASTRAL-2 study, genotype 2 patients were treated with 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) or sofosbuvir plus ribavirin ([Foster, 2015a](#)). Of the 266 participants, a minority (15%) had a history of previous peginterferon/ribavirin treatment failure and a similar proportion (14%) had compensated cirrhosis. Overall, the combination of sofosbuvir/velpatasvir yielded a statistically significant superior SVR12 of 99% vs 94% for sofosbuvir plus ribavirin. The only treatment failure in the sofosbuvir/velpatasvir arm was a patient who withdrew from the study after a single day due to side effects (anxiety). In contrast, there were 6 virologic failures in the sofosbuvir plus ribavirin arm. Fatigue and anemia were more commonly reported in patients receiving sofosbuvir plus ribavirin.

The phase 3 POLARIS-2 study randomized patients to 8 weeks of sofosbuvir/velpatasvir/voxilaprevir or 12 weeks of sofosbuvir/velpatasvir. Fifty-three genotype 2 patients were included in the sofosbuvir/velpatasvir arm and all achieved SVR (100%, 53/53) ([Jacobson, 2017](#)). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2, including those with a past peginterferon/ribavirin treatment failure and patients with compensated cirrhosis.

Considering the high SVR12 and fewer side effects with sofosbuvir/velpatasvir, regimens with peginterferon and/or ribavirin are no longer recommended for genotype 2.

### **Glecaprevir/Pibrentasvir**

The phase 3, single arm, open-label EXPEDITION-1 study investigated the safety and efficacy of a 12-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in patients with genotype 1, 2, 4, 5, or 6 and compensated cirrhosis ([Forns, 2017](#)). Treatment-naïve and -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) were included in the trial. Overall, only 25% (n=36) of patients were treatment experienced. The SVR12 in the genotype 2 patients was 100% (31/31). Overall, 91% percent (133/146) of patients had a Child-Pugh score of 5, and 9% (13/146) had a Child-Pugh score of 6. Twenty percent of patients had a platelet count <100 x 10<sup>9</sup>/L and all but 1 participant had a normal albumin level. In this patient population with compensated cirrhosis, the regimen was safe and well tolerated. There were 11 serious adverse events; none were DAA-related and no adverse events led to discontinuation of the study drugs. This is a safe and highly efficacious 12-week regimen in patients with well-compensated cirrhosis.

**Last update:** November 6, 2019

## **DAA-Experienced (Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures), Genotype 2 Patients, With or Without Compensated Cirrhosis**

(For [glecaprevir/pibrentasvir treatment failures](#), please see that topic.)

Recommended regimens listed by evidence level for:

### Sofosbuvir + Ribavirin-Experienced, Genotype 2 Patients, With or Without Compensated Cirrhosis<sup>a</sup> **i**

RECOMMENDED	DURATION	RATING <b>i</b>
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup>	12 weeks	IIb, B

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended regimen for:

### Sofosbuvir + NS5A Inhibitor-Experienced (Excluding Glecaprevir/Pibrentasvir Failures), Genotype 2 Patients, With or Without Compensated Cirrhosis<sup>a</sup> **i**

RECOMMENDED	DURATION	RATING <b>i</b>
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	I, B

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

## Sofosbuvir/Velpatasvir

The phase 3, open-label, randomized clinical trial POLARIS-4 compared a 12-week course of sofosbuvir/velpatasvir/voxilaprevir to 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in non-NS5A inhibitor DAA-experienced patients ([Bourliere, 2017](#)). Overall, 69% of patients were previously exposed to sofosbuvir plus ribavirin ± peginterferon, and 11% were exposed to sofosbuvir plus simeprevir. Cirrhosis was common, 46% in both study arms. Among patients with genotype 2, 97% (32/33) who received 12 weeks of sofosbuvir/velpatasvir achieved SVR12. Overall for the study, the sofosbuvir/velpatasvir arm did not meet the prespecified performance goal of > 85% efficacy (prespecified p value 0.025). However, this was primarily driven by treatment failure in patients with genotype 3 or 1a. The single genotype 2 patient who experienced virologic failure in the sofosbuvir/velpatasvir arm had virologic breakthrough rather than relapse and was the only patient with an NS5B RAS at any time point. The S292T substitution emerged at the time of virologic failure. Diarrhea and nausea were more commonly reported in the sofosbuvir/velpatasvir/voxilaprevir group.

## Glecaprevir/Pibrentasvir

The phase 3, randomized, double-blind, placebo-controlled ENDURANCE-2 study enrolled treatment-naïve or



-experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) noncirrhotic genotype 2 patients. Participants were treated with 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills or placebo ([Asselah, 2018b](#)). Among 202 patients in the glecaprevir/pibrentasvir arm, 30% (61/202) were treatment experienced, of whom 6 had previously received sofosbuvir plus ribavirin ± peginterferon. The overall SVR12 in the intention-to-treat analysis was 99%, and SVR12 was achieved in all 6 patients with a prior sofosbuvir-based treatment failure. The most common adverse events in the glecaprevir/pibrentasvir arm were headache and fatigue.

The phase 3, single arm, open-label EXPEDITION-1 study investigated the safety and efficacy of a 12-week course of glecaprevir/pibrentasvir in patients with genotype 1, 2, 4, 5, or 6 and compensated cirrhosis. Treatment-naïve and -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) were included in the trial. Overall, only 25% (n=36) of patients were treatment experienced, 11 of which had a history of sofosbuvir failure (although it is unclear how many of these patients had genotype 2). The SVR12 in the genotype 2 patients was 100% (31/31) ([Forns, 2017](#)).

No sofosbuvir treatment failures were included in the SURVEYOR study, which investigated 8 weeks of therapy in noncirrhotic patients with genotype 2. Thus, this regimen cannot be recommended in this patient population until supported by clinical data ([Poordad, 2017](#)).

### Sofosbuvir/Velpatasvir/Voxilaprevir

POLARIS-1 evaluated 12 weeks of sofosbuvir/velpatasvir/voxilaprevir compared to placebo among patients with all genotypes who were previously treated with an NS5A inhibitor-containing regimen (including daclatasvir and velpatasvir but not glecaprevir). There were 5 genotype 2 patients and all achieved SVR12 ([Bourliere, 2017](#)).

**Last update:** November 6, 2019

## Treatment-Experienced Genotype 3

The following pages include guidance for management of treatment-experienced patients with genotype 3 infection.

- [Peginterferon/Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis](#)
- [Peginterferon/Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis](#)
- [DAA-Experienced \(Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures\), Genotype 3 Patients, With or Without Compensated Cirrhosis](#)
- [Glecaprevir/Pibrentasvir Treatment Failures \(All Genotypes\)](#)
- [Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failure \(All Genotypes\)](#)

**Last update:** November 6, 2019

## Peginterferon/Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

## Peginterferon/Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING <sup>i</sup>
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for patients without baseline Y93H RAS to velpatasvir <sup>a</sup>	12 weeks	I, A
ALTERNATIVE	DURATION	RATING <sup>i</sup>
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup>	16 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) when Y93H is present	12 weeks	IIb, B

<sup>a</sup> Baseline RAS testing for Y93H is recommended. If the Y93H substitution is identified, an alternative regimen should be used, or weight-based ribavirin should be added.

<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

## Recommended Regimen

### Sofosbuvir/Velpatasvir

The phase 3 ASTRAL-3 study evaluated the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (without ribavirin) in 277 genotype 3-infected patients, including 71 with prior treatment experience and 80 with compensated cirrhosis ([Foster, 2015a](#)). Despite a high combined SVR12 of 95% (264/277), both prior treatment (90% SVR12) and compensated cirrhosis (91% SVR12) had a moderate negative impact on treatment response. The addition of ribavirin appeared to increase SVR12 rate in a phase 2 study that included treatment-experienced, genotype 3 patients treated for 12 weeks with sofosbuvir (400 mg) plus 25 mg or 100 mg of velpatasvir, with or without ribavirin ([Planko, 2015](#)).

The phase 3 POLARIS-2 study evaluated 12 weeks of sofosbuvir/velpatasvir versus 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in patients (any genotype) who were either treatment naive or had a previous peginterferon/ribavirin treatment failure. Eighty-nine genotype 3 patients (all without cirrhosis) received the sofosbuvir/velpatasvir regimen and 97% (86/89) achieved SVR12 ([Jacobson, 2017](#)). There were no virologic failures. These findings confirm the efficacy of this 12-week regimen in noncirrhotic genotype 3 patients.

Baseline NS5A substitutions in genotype 3 infection impact DAA treatment response, with the Y93H substitution having the greatest effect. In the ALLY-3 study, the Y93H substitution was detected at baseline in 9% (13/147) of participants ([Nelson, 2015](#)). SVR12 in these patients was 54% (7/13), including an SVR12 of 67% (6/9) in noncirrhotic patients. In the ASTRAL-3 study, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 of 84% (21/25) ([Foster, 2015a](#)).

Pending additional data, baseline NS5A RAS testing is recommended in all treatment-experienced, genotype 3 patients without cirrhosis for whom sofosbuvir/velpatasvir is being considered. If the Y93H substitution is identified, an alternative

regimen should be used, or weight-based ribavirin should be added.

## Alternative Regimens

### Glecaprevir/Pibrentasvir

The SURVEYOR-II, part 3 trial evaluated the safety and efficacy of a 12-week or 16-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in treatment-naïve or -experienced (standard or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon), genotype 3 patients without cirrhosis or with compensated cirrhosis. Among the 44 treatment-experienced patients without cirrhosis, the SVR12 rates were 91% (20/22) and 96% (21/22) for 12 weeks and 16 weeks, respectively. The 3 patients who experienced treatment failure had baseline RAS mutations. One patient in the 12-week study arm had an A30K RAS at baseline and a treatment-emergent Y93H RAS at failure resulting in the A30K+Y93H double RAS, which confers 69-fold resistance to glecaprevir/pibrentasvir. This was also true in the single relapse in the 16-week study arm. The second patient with relapse in the 12-week arm had a baseline Y93H RAS, which persisted at the time of failure. The Y93H substitution does not confer high-fold resistance to this regimen ([Wyles, 2018](#)).

Based on these data, the appropriate length of therapy is unclear for genotype 3, peginterferon/ribavirin-experienced patients. Until further data are available, a 16-week duration of treatment is recommended as an alternative option, especially if a baseline A30K substitution is present.

### Sofosbuvir/Velpatasvir/Voxilaprevir

The efficacy of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in genotype 3 patients is supported by the phase 3 POLARIS trials, which investigated 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in DAA-naïve patients and 12 weeks in DAA-experienced participants. The 8-week regimen achieved noninferiority compared to a 12-week sofosbuvir/velpatasvir regimen in the POLARIS-3 study, which included 35 interferon-experienced, cirrhotic patients with genotype 3 ([Jacobson, 2017](#)). Thus, this regimen is recommended as an alternative option for patients with genotype 3 who have evidence of the Y93H RAS at baseline.



In the ASTRAL-3 study, which investigated 12 weeks of sofosbuvir/velpatasvir, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 of 84% (21/25) ([Foster, 2015a](#)). Due to lack of an apparent adverse impact of Y93H in the context of triple-class drug therapy in the POLARIS-1 and -4 studies and the difficult-to-treat nature of treatment-experienced, genotype 3 patients, we recommend 12 weeks of sofosbuvir/velpatasvir/voxilaprevir to optimize SVR12 ([Sarrazin, 2018](#)).

**Last update:** November 6, 2019

## Peginterferon/Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

## Peginterferon/Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis<sup>a</sup>

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup>	16 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	IIb, B
ALTERNATIVE	DURATION	RATING 
Daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) plus weight-based ribavirin	12 weeks	II, B

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

## Recommended Regimens

### Glecaprevir/Pibrentasvir

The SURVEYOR-II, part 3 trial evaluated the safety and efficacy of a 12-week or 16-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in treatment-naïve or -experienced (standard or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon), genotype 3 patients without cirrhosis or with compensated cirrhosis. Among the 47 treatment-experienced participants with compensated cirrhosis who were treated for 16 weeks, the SVR12 was 96% (45/47). One of the virologic failures was a relapse and the other was a viral breakthrough. The patient with viral breakthrough had low serum DAA levels at week 4 of the study, suggesting poor adherence. The patient with relapse did not have baseline NS3 or NS5A RASs but did have dual NS5A RASs emerge at the time of failure ([Wyles, 2018](#)). Sixteen weeks of glecaprevir/pibrentasvir is a recommended regimen for peginterferon/ribavirin-experienced patients with cirrhosis and genotype 3 given the high SVR and lack of need for the addition of ribavirin to the regimen.

### Sofosbuvir/Velpatasvir/Voxilaprevir

The efficacy of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in genotype 3 patients is supported by the phase 3 POLARIS trials, which investigated 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in DAA-naïve patients and 12 weeks in DAA-experienced patients. The 8-week regimen achieved a 96% SVR, which was noninferior to a 12-week sofosbuvir/velpatasvir regimen in the POLARIS-3 study, which included 35 interferon-experienced, cirrhotic patients with genotype 3 ([Jacobson, 2017](#)). Thus, this regimen is recommended in cirrhotic patients with genotype 3.

## Alternative Regimens

### Elbasvir/Grazoprevir + Sofosbuvir

The C-ISLE study evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir, with or without ribavirin, for 8 weeks to 16 weeks among treatment-naïve or -experienced, genotype 3 patients with compensated cirrhosis. One hundred patients were enrolled, including 53 with a history peginterferon/ribavirin failure. Treatment-experienced participants were randomized to 12 weeks of elbasvir/grazoprevir plus sofosbuvir, 12 weeks of elbasvir/grazoprevir plus sofosbuvir and weight-based ribavirin, or 16 weeks of elbasvir/grazoprevir plus sofosbuvir ([Foster, 2016b](#)). All 3 arms had 100% SVR on the per protocol analysis, with 17 patients in each arm. The efficacy was high regardless of the presence of baseline RASs, including 3 patients with the Y93H substitution.

### Sofosbuvir/Velpatasvir + Ribavirin

The phase 3 ASTRAL-3 study evaluated the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (without ribavirin) in 277 genotype 3 patients, including 71 with prior treatment experience and 80 with compensated cirrhosis ([Foster, 2015a](#)). Despite a high combined SVR12 of 95% (264/277), prior treatment (90% SVR12), Y93H substitution RAS (84% SVR12), and compensated cirrhosis (91% SVR12) had a moderate negative impact on treatment response. Among those with both compensated cirrhosis and prior treatment, the SVR12 was 89% (33/37). Similarly, in the POLARIS-3 study among peginterferon/ribavirin-experienced, cirrhotic genotype 3 patients treated for 12 weeks with sofosbuvir/velpatasvir, the SVR12 was 91% (29/32). ([Jacobson, 2017](#)).

The addition of ribavirin to the combination of sofosbuvir/velpatasvir was evaluated in genotype 3, cirrhotic patients ([Esteban, 2018](#)). In this study, 91% (92/101) of patients achieved SVR12 when treated with sofosbuvir/velpatasvir alone compared to 96% (99/103) of patients achieving SVR12 when ribavirin was added to the regimen. The largest benefit of the addition of ribavirin was seen in patients with baseline NS5A RAS with 84% (16/19) achieving SVR12 in the sofosbuvir/velpatasvir group compared to an SVR12 of 95% (21/22) in the sofosbuvir/velpatasvir plus ribavirin group. There were relatively small numbers of treatment-experienced patients enrolled in this study (27% overall). However, among the peginterferon/ribavirin-experienced patients, 93% (13/14) treated with sofosbuvir/velpatasvir achieved SVR12 whereas all 18 patients treated with sofosbuvir/velpatasvir plus ribavirin achieved SVR12.

Cirrhotic patients with genotype 3 and a prior non-DAA treatment failure are among the most difficult to treat. For this reason, ribavirin is recommended for all patients receiving sofosbuvir/velpatasvir, making this an alternative regimen.

**Last update:** November 6, 2019

## DAA-Experienced (Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures), Genotype 3 Patients, With or Without Compensated Cirrhosis

(For [glecaprevir/pibrentasvir treatment failures](#), please see that topic.)



Recommended regimens by evidence level for:

### Sofosbuvir + Ribavirin-Experienced ( $\pm$ Peginterferon), Genotype 3 Patients, With or Without Compensated Cirrhosis<sup>a</sup>

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg)	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup>	16 weeks	IIb, B

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended regimen for:

### DAA-Experienced (Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures), Genotype 3 Patients, With or Without Compensated Cirrhosis<sup>a</sup>

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	I, A
<hr/>		
For patients with prior NS5A inhibitor failure and cirrhosis, addition of weight-based ribavirin is recommended.	12 weeks	IIa, C

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

## Sofosbuvir/Velpatasvir/Voxilaprevir $\pm$ Ribavirin

The phase 3 POLARIS-1 and POLARIS-4 trials included patients with genotype 3, without cirrhosis or with compensated cirrhosis, who had previously received a DAA regimen, with or without an NS5A inhibitor. The POLARIS-4 study included treatment-experienced patients who had previously received a DAA regimen but not an NS5A inhibitor. Participants were randomized to 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) (54 with genotype 3) or 12 weeks of sofosbuvir/velpatasvir (52 with genotype 3). SVR12 rates for the genotype 3 patients were 96% (52/54) and 85% (44/52), respectively. The 8 patients who experienced a relapse in the sofosbuvir/velpatasvir arm were primarily white males with compensated cirrhosis (7/8) and a high BMI (>25). Although none had baseline Y93H variants, all had emergence of Y93H variants at the time of relapse ([Bourliere, 2017](#)). Seven of 8 failures were treated previously with sofosbuvir plus ribavirin, with or without interferon. Thus, in contrast to genotype 2,

sofosbuvir/velpatasvir is not recommended for retreatment of genotype 3 patients with prior exposure to sofosbuvir plus ribavirin, with or without interferon.

The POLARIS-1 study included patients who had previously received a regimen containing an NS5A inhibitor. Participants were randomized to 12 weeks of sofosbuvir/velpatasvir/voxilaprevir (78 with genotype 3) versus placebo. The SVR12 was 95% (74/78) for the genotype 3 patients. All 4 patients who experienced a relapse had cirrhosis ([Bourliere, 2017](#)). These data support the use of sofosbuvir/velpatasvir/voxilaprevir for 12 weeks in all DAA-experienced patients. In NS5A inhibitor-experienced genotype 3 patients with cirrhosis, however, the relapse rate is higher and adding weight-based ribavirin is recommended to minimize relapse risk.

## Glecaprevir/Pibrentasvir

The SURVEYOR-II, part 3 trial evaluated the safety and efficacy of a 12-week or 16-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in treatment-naïve or -experienced (standard or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon), genotype 3 patients without cirrhosis or with compensated cirrhosis. Among the 34 treatment-experienced participants with prior exposure to sofosbuvir who were treated for 16 weeks, regardless of cirrhosis status, SVR12 was 97% (33/34). The lone virologic failure was a relapse in a patient with cirrhosis. No NS5A RASs were present prior to treatment, however the L31F and Y93H substitutions were present at retreatment failure ([Wyles, 2018](#)). Sixteen weeks of glecaprevir/pibrentasvir is a recommended regimen for genotype 3 patients with prior exposure to sofosbuvir plus ribavirin given the high SVR and lack of need for addition of ribavirin to the regimen.

**Last update:** November 6, 2019

## Treatment-Experienced Genotype 4

The following pages include guidance for management of treatment-experienced patients with genotype 4 infection.

- [Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis](#)
- [Peginterferon/Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis](#)
- [DAA-Experienced \(Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures\), Genotype 4 Patients, With or Without Compensated Cirrhosis](#)
- [Glecaprevir/Pibrentasvir Treatment Failures \(All Genotypes\)](#)
- [Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failure \(All Genotypes\)](#)

**Last update:** November 6, 2019

## Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

## Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING <sup>i</sup>
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>a</sup>	8 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients who experienced virologic relapse after prior peginterferon/ribavirin therapy <sup>b</sup>	12 weeks	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B

<sup>a</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

<sup>b</sup> If the type of prior treatment failure (relapse vs breakthrough/nonresponse) is unknown, another recommended regimen should be used.

### Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naïve or -experienced patients with genotype 1, 2, 4, 5, or 6 treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks ([Feld, 2015](#)). The study included 116 patients with genotype 4. One hundred percent SVR12 was achieved, including 52 treatment-experienced patients ([Feld, 2015](#)).

### Glecaprevir/Pibrentasvir

The phase 2, open-label, single arm SURVEYOR-II, part 4 study investigated the efficacy of 8 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in noncirrhotic patients with genotype 2, 4, 5, or 6. Patients were treatment naïve or experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). Forty-six genotype 4 patients accounted for 23% of the study population; only 27 of these patients (13% of the study population) were treatment experienced. The SVR12 was 93%; 3 patients had nonvirologic outcomes, including missed follow-up and study discontinuation. There were no virologic failures but the number of treatment-experienced patients was small ([Asselah, 2018b](#)).

### Elbasvir/Grazoprevir ± Ribavirin

A 2015 integrated analysis of all phase 2 and phase 3 elbasvir (50 mg)/grazoprevir (100 mg) studies to date demonstrated efficacy of this regimen for both treatment-naïve (n=66) and -experienced (n=37) patients with genotype 4 ([Asselah, 2018c](#)). The overall SVR12 among treatment-experienced, genotype 4 patients was 87% (32/37) with numerical response differences based on prior interferon treatment response (relapse vs on-treatment viral failure); elbasvir/grazoprevir duration (12 weeks vs 16 weeks); and/or ribavirin usage (inclusion or exclusion of ribavirin in the regimen). Numbers within any specific subgroup are too small to make definitive recommendations. Trends emerged, however, that were

used to guide the current recommendations pending additional data. No treatment failures were seen in patients who relapsed after prior peginterferon/ribavirin therapy, regardless of elbasvir/grazoprevir treatment duration or ribavirin usage. In contrast, response rates were numerically lower in patients with prior on-treatment virologic failure in the non-ribavirin-containing arms (12 weeks, 78%; 16 weeks, 60%) compared to ribavirin-containing treatment (12 weeks with ribavirin, 91%; 16 weeks with ribavirin, 100%).




Given the lack of sufficient numbers to differentiate response between 12 weeks with ribavirin and 16 weeks with ribavirin, the use of 16 weeks of elbasvir/grazoprevir plus ribavirin in genotype 4 patients with prior on-treatment virologic failure represents the most conservative approach.

### Ledipasvir/Sofosbuvir

In the open-label cohort, phase 2a SYNERGY trial, 21 patients with genotype 4 were treated with a 12-week course of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg). Forty percent of participants were treatment experienced and 40% had advanced fibrosis. Twenty patients completed the 12-week therapy and all achieved SVR12; 1 patient withdrew from the study ([Kohli, 2015](#)). A pooled analysis of the 12-week ledipasvir/sofosbuvir regimen (including the SYNERGY trial) reported an SVR12 of 94% (32/34) in treatment-experienced patients with genotype 4 ([Asselah, 2018b](#)).

Last update: November 6, 2019

## Peginterferon/Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:		
Peginterferon/Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis <sup>a</sup> 		
RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients who experienced virologic relapse after prior peginterferon/ribavirin therapy <sup>b</sup>	12 weeks	IIa, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>c</sup>	12 weeks	IIa, B
ALTERNATIVE	DURATION	RATING 
Daily ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	IIa, B

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

<sup>b</sup> If the type of prior treatment failure (relapse vs breakthrough/nonresponse) is unknown, another recommended regimen should be used.

<sup>c</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended and alternative regimens listed by evidence level and alphabetically for:

## Peginterferon/Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis<sup>a</sup>

### Recommended Regimens

#### Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naïve or -experienced patients with genotype 1, 2, 4, 5, or 6 treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks ([Feld, 2015](#)). The study included 116 patients with genotype 4. One hundred percent SVR12 was achieved, including 52 treatment-experienced patients and 27 with compensated cirrhosis ([Feld, 2015](#)).

#### Elbasvir/Grazoprevir ± Ribavirin

A 2015 integrated analysis of all phase 2 and phase 3 elbasvir (50 mg)/grazoprevir (100 mg) studies to date demonstrated efficacy of this regimen for both treatment-naïve (n=66) and -experienced (n=37) patients with genotype 4 ([Asselah, 2018c](#)). The overall SVR12 among treatment-experienced, genotype 4 patients was 87% (32/37) with numerical response differences based on prior interferon treatment response (relapse vs on-treatment viral failure); elbasvir/grazoprevir duration (12 weeks vs 16 weeks); and/or ribavirin usage (inclusion or exclusion of ribavirin in the regimen). Numbers within any specific subgroup are too small to make definitive recommendations. Trends emerged, however, that were used to guide the current recommendations pending additional data. No treatment failures were seen in patients who relapsed after prior peginterferon/ribavirin therapy, regardless of elbasvir/grazoprevir treatment duration or ribavirin usage. In contrast, response rates were numerically lower in patients with prior on-treatment virologic failure in the non-ribavirin-containing arms (12 weeks, 78%; 16 weeks, 60%) compared to ribavirin-containing treatment (12 weeks with ribavirin, 91%; 16 weeks with ribavirin, 100%).

Given the lack of sufficient numbers to differentiate response between 12 weeks with ribavirin and 16 weeks with ribavirin, the use of 16 weeks of elbasvir/grazoprevir plus ribavirin in genotype 4 patients with prior on-treatment virologic failure represents the most conservative approach and is an alternative recommendation.

#### Glecaprevir/Pibrentasvir

The phase 3, single-arm, open-label EXPEDITION-1 study investigated the safety and efficacy of a 12-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in patients with genotype 1, 2, 4, 5, or 6 and compensated cirrhosis ([Forns, 2017](#)). Overall, 25% of patients were treatment experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). All 16 patients with genotype 4 (unknown number with prior treatment experience) achieved SVR12.

### Alternative Regimen

#### Ledipasvir/Sofosbuvir + Ribavirin



In the open-label cohort, phase 2a SYNERGY trial, 21 patients with genotype 4 were treated with a 12-week course of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg). Forty percent of participants were treatment experienced and 40% had advanced fibrosis. Twenty patients completed the 12-week therapy and all achieved SVR12; 1 patient withdrew from the study ([Kohli, 2015](#)). A pooled analysis of the 12-week ledipasvir/sofosbuvir regimen (including the SYNERGY trial) reported an SVR12 of 94% (32/34) in treatment-experienced patients with genotype 4 ([Asselah,](#)

[2018b](#)). Due to the small number of patients overall and with cirrhosis, the addition of ribavirin to the 12-week regimen is recommended in patients with cirrhosis ([Kohli, 2015](#)). This is an alternative regimen due to the need for ribavirin.

**Last update:** November 6, 2019

## DAA-Experienced (Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures), Genotype 4 Patients, With or Without Compensated Cirrhosis

(For [glecaprevir/pibrentasvir treatment failures](#), please see that topic.)

Recommended regimen for:		
DAA-Experienced (Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures), Genotype 4 Patients, With or Without Compensated Cirrhosis <sup>a</sup> 		
RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	I, A
<sup>a</sup> For <a href="#">decompensated cirrhosis</a> , please refer to the appropriate section.		

### Sofosbuvir/Velpatasvir/Voxilaprevir

The phase 3 POLARIS-1 and POLARIS-4 trials included patients with genotype 4, with or without compensated cirrhosis, who had previously received a DAA regimen, with or without an NS5A inhibitor. The trials included 22 genotype 4 patients with a prior treatment failure with an NS5A inhibitor-containing DAA regimen, and 19 genotype 4 patients with a prior treatment failure with a DAA regimen not containing an NS5A inhibitor. The study evaluated the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for 12 weeks. Overall, 46% of patients in these clinical trials had compensated cirrhosis, although the number of genotype 4 patients with cirrhosis was not provided. Among the 22 patients who had a prior treatment failure with an NS5A inhibitor-containing regimen, 91% (20/22) achieved SVR; 1 patient relapsed and another experienced treatment failure for nonvirologic reasons. All patients with a history of treatment failure with a DAA regimen not containing an NS5A inhibitor achieved SVR (19/19, 100%) ([Bourliere, 2017](#)).



Last update: November 6, 2019



## Treatment-Experienced Genotype 5 or 6

The following pages include guidance for management of treatment-experienced patients with genotype 5 or 6 infection.

- [Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Patients With or Without Compensated Cirrhosis](#)
- [DAA-Experienced \(Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures\), Genotype 5 or 6 Patients, With or Without Compensated Cirrhosis](#)
- [Glecaprevir/Pibrentasvir Treatment Failures \(All Genotypes\)](#)
- [Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failure \(All Genotypes\)](#)

Last update: November 6, 2019

## Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Patients With or Without Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:		
Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Patients, With or Without Compensated Cirrhosis <sup>a</sup> 		
RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup> for patients without cirrhosis	8 weeks	Ila, B
<hr/>		
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup> for patients with compensated cirrhosis	12 weeks	I, B
Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	Ila, B

Recommended regimens listed by evidence level and alphabetically for:

## Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Patients, With or Without Compensated Cirrhosis<sup>a</sup> **i**

Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	Ila, B
--	----------	--------

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

### Glecaprevir/Pibrentasvir

A combined analysis of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 8 weeks or 12 weeks among 2,041 patients participating in phase 2 and phase 3 clinical trials included 30 patients with genotype 5 and 44 with genotype 6 ([Puoti, 2018](#)). Approximately 22% of patients in the overall study had a prior interferon-based treatment failure; DAA failures other than with sofosbuvir were excluded. No patients had cirrhosis. SVR rates among treatment-naïve or -experienced, genotype 5 participants were 100% (2/2) for those receiving 8 weeks of glecaprevir/pibrentasvir and 100% (28/28) for those receiving 12 weeks of glecaprevir/pibrentasvir. SVR rates among treatment-naïve or -experienced, genotype 6 participants were 92% (12/13) for those receiving 8 weeks of glecaprevir/pibrentasvir and 100% (31/31) among those receiving 12 weeks of glecaprevir/pibrentasvir. The single treatment failure in the 8-week group was a nonvirologic failure.

### Ledipasvir/Sofosbuvir

Ledipasvir has in vitro activity against most genotype 6 subtypes, except 6e ([Wong, 2013](#)); ([Kohler, 2014](#)). A small, 2-center, open-label study (NCT01826981) investigated the safety and efficacy of a 12-week course of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in treatment-naïve or -experienced patients with genotype 6. Twenty-five patients (92% treatment naïve) who were primarily of Asian descent (88%) were infected with different genotype 6 subtypes (n=8 6a; n=6 6e; n=3 6l; n=2 6m; n=3 6p; n=2 6q; n=1 6r). Two patients (8%) had compensated cirrhosis. The SVR12 was 96% (24/25). The single patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment due to adverse events ([Gane, 2015](#)).

Similarly, 41 patients with genotype 5 were treated with 12 weeks of ledipasvir/sofosbuvir. The group included both treatment-naïve and -experienced patients, with and without cirrhosis. SVR was 93% (38/41) ([Abergel, 2016](#)).



### Sofosbuvir/Velpatasvir

Velpatasvir has in vitro activity against genotypes 5 and 6. The ASTRAL-1 study included 35 patients with genotype 5 and 41 patients with genotype 6. Among those participants, only 11 and 3, respectively, were treatment experienced ([Feld, 2015](#)). All genotype 5 and 6, treatment-experienced patients treated with 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) achieved SVR12.

Last update: November 6, 2019

## DAA-Experienced (Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures), Genotype 5 or 6 Patients, With or Without Compensated Cirrhosis

(For [glecaprevir/pibrentasvir treatment failures](#), please see that topic.)

Recommended regimen for:		
<b>DAA-Experienced (Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures), Genotype 5 or 6 Patients, With or Without Compensated Cirrhosis<sup>a</sup> </b>		
RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	Ila, B
<sup>a</sup> For <a href="#">decompensated cirrhosis</a> , please refer to the appropriate section.		

### Sofosbuvir/Velpatasvir/Voxilaprevir


Minimal data are available from phase 3 clinical trials regarding the efficacy of a 12-week course of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) among patients with genotype 5 or 6 and a history of treatment failure with a DAA-containing regimen. All 7 patients with genotype 5 or 6 (1 genotype 5; 6 genotype 6) participating in the phase 3 POLARIS-1 trial achieved SVR. All participants enrolled in the study had a prior treatment failure with an NS5A inhibitor-containing regimen. Forty-six percent had compensated cirrhosis, although the percentage of patients with genotype 5 or 6 infection with cirrhosis was not provided ([Bourliere, 2017](#)).

Last update: November 6, 2019

## Glecaprevir/Pibrentasvir Treatment Failure (All Genotypes)

Recommended regimens listed by evidence level and alphabetically for:

## Patients With Prior Glecaprevir/Pibrentasvir Treatment Failure (All Genotypes), With or Without Compensated Cirrhosis<sup>a</sup>

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup> plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks	Ila, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	Ila, B
<hr/>		
For patients with compensated cirrhosis, addition of weight-based ribavirin is recommended.	12 weeks	Ila, C

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.  
<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

### Glecaprevir/Pibrentasvir Plus Sofosbuvir and Ribavirin

For the small number of patients in whom treatment with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) fails, the addition of ribavirin and sofosbuvir is an attractive retreatment option. MAGELLAN-3 is an ongoing phase 3b study evaluating the safety and efficacy of glecaprevir/pibrentasvir in combination with sofosbuvir (400 mg) and weight-based ribavirin as a 12- or 16-week retreatment regimen for patients who experienced virologic failure to glecaprevir/pibrentasvir within the context of a previous AbbVie clinical trial ([Wyles, 2019](#)). Noncirrhotic glecaprevir/pibrentasvir nonresponders with genotype 1, 2, 4, 5, or 6 who were naive to protease and NS5A inhibitors received 12 weeks glecaprevir/pibrentasvir plus sofosbuvir and weight-based ribavirin. Patients with genotype 3, and/or compensated cirrhosis, and/or protease/NS5A experience (prior to their initial glecaprevir/pibrentasvir treatment) received 16 weeks of therapy with the same regimen. In a preliminary analysis, 96% (22/23) of these patients achieved SVR12 with a single relapse in a cirrhotic patient with genotype 1a. Although the number of patients was relatively small and the study population heterogeneous, the presence of baseline RASs did not appear to substantively affect response rates. This study provides the rationale to recommend the combination of glecaprevir/pibrentasvir plus sofosbuvir and ribavirin for 16 weeks for the few patients in whom initial treatment with glecaprevir/pibrentasvir fails.

### Sofosbuvir/Velpatasvir/Voxilaprevir

A prospective, nonrandomized observational study of patients in whom treatment with glecaprevir/pibrentasvir failed examined the utility of retreatment with 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) ([Pearlman, 2019](#)). SVR12 was achieved in 94% (29/31) of the patients. The cohort had higher proportions of patients traditionally associated with virologic failure, including black race, cirrhosis, and genotype 3.


Two patients relapsed at week 4 following completion of therapy. The first patient had genotype 3 infection, was noncirrhotic, and had a A30K mutation at baseline and at relapse. The other patient had genotype 1a infection, compensated cirrhosis, a Y93 variant detected at baseline, and L31M and Y93 variants at relapse. The addition of ribavirin was not evaluated in this study. However, for patients with cirrhosis, it may be helpful to add ribavirin based on prior studies of DAA failures.

**Last update:** November 6, 2019

## Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failure (All Genotypes)

Recommended regimens listed by evidence level and alphabetically for:

### Patients With Prior Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failure (All Genotypes), With or Without Compensated Cirrhosis<sup>a</sup>

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup> plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks	Ila, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) plus weight-based ribavirin	24 weeks	Ila, B

<sup>a</sup> For [decompensated cirrhosis](#), please refer to the appropriate section.

<sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

### Glecaprevir/Pibrentasvir Plus Sofosbuvir and Ribavirin

There are no studies examining retreatment of patients in whom therapy with sofosbuvir/velpatasvir/voxilaprevir failed. However, pibrentasvir has improved in vitro activity compared to other NS5A inhibitors against most NS5A RASs ([Ng, 2017b](#)). A small study demonstrated the efficacy of glecaprevir/pibrentasvir plus sofosbuvir and ribavirin for heavily DAA-experienced patients (including those with genotype 3 and/or cirrhosis), although no sofosbuvir/velpatasvir/voxilaprevir failures were included ([Wyles, 2019](#)). Sixteen weeks of glecaprevir/pibrentasvir plus sofosbuvir and ribavirin is recommended based on the improved resistance profile of pibrentasvir and high response rate seen with this duration of therapy among genotype 3 patients in the MAGELLAN-3 trial ([Wyles, 2019](#)). Extension to 24 weeks with this regimen could be considered but there are currently no clinical data to support such an approach.

## Sofosbuvir/Velpatasvir/Voxilaprevir Plus Ribavirin

Although there are no studies examining retreatment of patients in whom therapy with sofosbuvir/velpatasvir/voxilaprevir failed, in the POLARIS-1 study—which studied sofosbuvir/velpatasvir/voxilaprevir treatment among patients who had a prior DAA therapy failure—treatment failure with this triple antiviral regimen was seen more commonly in cirrhotic patients (7% vs 1% in noncirrhotics), those with genotype 3 (5% vs 0% in genotype 1), and those with genotype 4 (9% vs 0% in genotype 1) ([Bourliere, 2017](#)). Pre-existing RASs did not affect SVR nor did failure select for additional RAS variants. The recommendation to treat with longer therapy in conjunction with ribavirin when retreating with the same DAA regimen (sofosbuvir/velpatasvir/voxilaprevir) is based on extrapolation from prior studies showing benefit with this strategy in different populations ([Gane, 2017](#)).

**Last update:** November 6, 2019

### Related References

- Abergel A, Asselah T, Metivier S, Loustaud-Ratti V. [Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study](#). *Lancet Infect Dis*. 2016;16(4):459-464.
- Afdhal NH, Reddy KR, Nelson DR, Lawitz EJ, Gordon SC, Schiff ER, et al. [Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection](#). *N Engl J Med*. 2014;370(16):1483-1493.
- Asselah T, Kowdley KV, Zadeikis N, Wang S, Hassanein T, Horsmans Y, et al. [Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2, 4, 5, or 6 infection without cirrhosis](#). *Clin Gastroenterol Hepatol*. 2018;16(3):417-426.
- Asselah T, Reesink H, Gerstoft J, et al. [Efficacy of elbasvir and grazoprevir in participants with hepatitis C virus genotype 4 infection: a pooled analysis](#). *Liver Int*. 2018;38(9):1583-1591.
- Bourliere M, Bronowicki J, de Ledinghen V, Hézode C, Zoulim F, Mathurin P, et al. [Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial \(SIRIUS\)](#). *Lancet Infect Dis*. 2015;15(4):397-404.
- Bourliere M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, et al. [Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection](#). *N Engl J Med*. 2017;376(22):2134-2146.
- Braun DL, Hampel B, Kouyos R, et al. [High cure rates with grazoprevir-elbasvir with or without ribavirin guided by genotypic resistance testing among human immunodeficiency virus/hepatitis C virus-coinfected men who have sex with men](#). *Clin Infect Dis*. 2019;68(4):569-576.
- Esteban R, Pineda JA, Calleja JL, et al. [Efficacy of sofosbuvir and velpatasvir, with and without ribavirin, in patients with hepatitis C virus genotype 3 infection and cirrhosis](#). *Gastroenterology*. 2018;155(4):1120-1127.e4.
- Feld JJ, Jacobson IM, Hézode C, Asselah T, Ruane PJ, Gruener N, et al. [Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection](#). *N Engl J Med*. 2015;373(27):2599-2607.
- Forns X, Gordon SC, Zuckerman E, Lawitz E, Calleja JL, Hofer H, et al. [Grazoprevir and elbasvir plus ribavirin for chronic](#)



[HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent.](#) J Hepatol. 2015;63(3):564-572.

Forns X, Lee SS, Valdes J, Lens S, Ghalib R, Aguilar H, et al. [Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis \(EXPEDITION-1\): a single-arm, open-label, multicentre phase 3 trial.](#) Lancet Infect Dis. 2017;17(10):1062-1068.

Foster GR, Afdhal NH, Roberts SK. [Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection.](#) N Engl J Med. 2015;373(27):2608-2617.

Foster GR, Agarwal K, Cramp M, Moreea S, Barclay ST, Collier J, et al. [C-ISLE: Grazoprevir/Elbasvir plus Sofosbuvir in Treatment-naive and Treatment-experienced HCV GT3 Cirrhotic Patients Treated for 8, 12 or 16 weeks \[Abstract 74\].](#) In The Liver Meeting. 2016.

Gane EJ, Hyland RH, An D, Svarovskaia ES, Pang PS, Brainard D, et al. [Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection.](#) Gastroenterology. 2015;149(6):1454-1461.

Gane EJ, Shiffman ML, Etzkorn K, et al, et al. [Sofosbuvir-velpatasvir with ribavirin for 24 weeks in hepatitis C virus patients previously treated with a direct-acting antiviral regimen.](#) Hepatology. 2017;66(4):1083-1089.

Howe AY, Black S, Curry S, Ludmerer SW, Liu R, Barnard RJO, et al. [Virologic resistance analysis from a phase 2 study of MK-5172 combined with pegylated interferon/ribavirin in treatment-naive patients with hepatitis C virus genotype 1 infection.](#) Clin Infect Dis. 2014;59(12):1657-1665.

Jacobson IM, Asante-Appiah E, Wong P, Black T, Howe A, Wahl J, et al. [Prevalence and impact of baseline NSA resistance associated variants \(RAVs\) on the efficacy of elbasvir/grazoprevir \(EBR/GZR\) against GT1a infection \[abstract LB-22\].](#) The Liver Meeting. San Francisco, CA; 2015.

Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG, et al. [Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials.](#) Gastroenterology. 2017;153(1):113-122.

Kohler JJ, Nettles JH, Amblard F, Hurwitz SJ, Bassit L, Stanton RA, et al. [Approaches to hepatitis C treatment and cure using NS5A inhibitors.](#) Infect Drug Resist. 2014;7:41-56.

Kohli A, Kapoor R, Sims Z, Nelson A, Sidharthan S, Lam B, et al. [Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study.](#) Lancet Infect Dis. 2015;15(9):1049-1054.

Kwo PY, Gane EJ, Peng C-Y, et al. [Efficacy and safety of grazoprevir/elbasvir +/- RBV for 12 weeks in patients with HCV G1 or G4 infection who previously failed peginterferon/RBV: C-EDGE treatment-experienced trial \[P0886\].](#) J Hepatol. 2015;62(Suppl 2):S674-S675.

Kwo PY, Gane EJ, Peng CY, Pearlman B, Vierling JM, Serfaty L, et al. [Effectiveness of elbasvir and grazoprevir combination, with or without ribavirin, for treatment-experienced patients with chronic hepatitis C infection.](#) Gastroenterology. 2017;152(1):164-175.e4.

Nelson DR, Cooper JN, Lalezari JP, et al. [All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study.](#) Lawitz EJ, Pockros PJ, Gitlin N, Freilich BF, Younes ZH, Harlan W, et al. Hepatology. 2015;61(4):1127-1135.

- Ng TI, Krishnan P, Pilot-Matias T, et al. [In vitro antiviral activity and resistance profile of the next-generation hepatitis C virus NS5A inhibitor pibrentasvir](#). *Antimicrob Agents Chemother*. 2017;61(5):pii: e02558-16.
- Osinusi A, Kohli A, Marti MM, Nelson A, Zhang X, Meissner EG, et al. [Re-treatment of chronic hepatitis C virus genotype 1 infection after relapse: an open-label pilot study](#). *Ann Intern Med*. 2014;161(9):634-638.
- Pearlman B, Perrys M, Hinds A. [Sofosbuvir/velpatasvir/voxilaprevir for previous treatment failures with glecaprevir/pibrentasvir in chronic hepatitis C infection](#). *Am J Gastroenterol*. San Francisco, CA; 2019;114(9):1550-1552.
- Pianko S, Flamm SL, Shiffman ML, et al. [Sofosbuvir plus velpatasvir combination therapy for treatment-experienced patients with genotype 1 or 3 hepatitis C virus infection: a randomized trial](#). Kumar S, Strasser SI, Dore GJ, McNally J, Brainard DM, Han L, et al. *Ann Intern Med*. 2015;163(11):809-817.
- Poordad F, Felizarta F, Asatryan A, et al. [Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment](#). Sulkowski MS, Reindollar RW, Landis CS, Gordon SC, Flamm SL, Fried MW, et al. *Hepatology*. 2017;66(2):389-397.
- Poordad F, Pol S, Asatryan A, et al. [MAGELLAN-1, part 2: glecaprevir and pibrentasvir for 12 or 16 weeks in patients with chronic HCV genotype 1 or 4 and prior direct-acting antiviral treatment failure](#). Buti M, Shaw DR, Hezode C, Lalezari J, Felizarta F, Reindollar R, et al. *Gastroenterology*. 2017;152(5):S1057.
- Puoti M, Foster GR, Wang S, et al. [High SVR12 with 8-week and 12-week glecaprevir/pibrentasvir therapy: An integrated analysis of HCV genotype 1-6 patients without cirrhosis](#). *J Hepatol*. 2018;69(2):293-300.
- Reddy KR, Bourliere M, Sulkowski MS, et al. [Ledipasvir and sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: An integrated safety and efficacy analysis](#). Omata M, Zeuzem S, Feld JJ, Lawitz EJ, Marcellin P, Welzel TM, et al. *Hepatology*. 2015;62(1):79-86.
- Sarrazin C, Cooper CL, Manns MP, et al. [No impact of resistance-associated substitutions on the efficacy of sofosbuvir, velpatasvir, and voxilaprevir for 12 weeks in HCV DAA-experienced patients](#). *J Hepatol*. 2018;69(6):1221-1230.
- Summa V, Ludmerer SW, McCauley JA, et al. [MK-5172, a selective inhibitor of hepatitis C virus NS3/4a protease with broad activity across genotypes and resistant variants](#). *Antimicrob Agents Chemother*. 2012;56(8):4161-4167.
- Wong KA, Worth A, Martin R, Svarovskaia ES, Brainard DM, Lawitz EJ, et al. [Characterization of Hepatitis C virus resistance from a multiple-dose clinical trial of the novel NS5A inhibitor GS-5885](#). *Antimicrob Agents Chemother*. 2013;57(12):6333-6340.
- Wyles DL, Pockros P, Morelli G, Younes Z, Svarovskaia ES, Yang JC, et al. [Ledipasvir-sofosbuvir plus ribavirin for patients with genotype 1 hepatitis C virus previously treated in clinical trials of sofosbuvir regimens](#). *Hepatology*. 2015;61(6):1793-1797.
- Wyles D, Poordad F, Wang S, Alric L, Felizarta F, Kwo PY, et al. [Glecaprevir/pibrentasvir for hepatitis C virus genotype 3 patients with cirrhosis and/or prior treatment experience: a partially randomized phase 3 clinical trial: viral hepatitis](#). *Hepatology*. 2018;67(2):514-523.
- Wyles D, Weiland O, Yao B, et al. [Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection](#). *J Hepatol*. 2019;70(5):1019-1023.

Zeuzem S, Rockstroh JK, Kwo PY, et al. [Predictors of response to grazoprevir/elbasvir among HCV genotype 1 \(GT1\)-infected patients: integrated analysis of phase 2-3 trials \[abstract 700\]](#). In Liver Meeting 2015. San Francisco, CA; 2015.

Zeuzem S, Feld J, Wang S. [ENDURANCE-1: efficacy and safety of 8- versus 12-week treatment with ABT-493/ABT-530 in patients with chronic HCV genotype 1 infection \[abstract 253\]](#). In The Liver Meeting 2016. Boston, MA; 2016.

Zeuzem S, Mizokami M, Pianko S, Mangia A, Han KH, Martin R, et al. [NS5A resistance-associated substitutions in patients with genotype 1 hepatitis C virus: prevalence and effect on treatment outcome](#). J Hepatol. 2017;66(5):910-918.